Acta Genetica et Statistica Medica

Vol. 11, No. 2 — 1961

BASEL (Schweiz) — S. KARGER — NEW YORK

Printed in Switzerland

Acta genet.

INDEX

«Acta Genetica et Statistica Medica» paraît trimestriellement en fascicules de 96 pages environ. Le prix annuel d'un abonnement est de fr. s. 56.— frais de port inclus.

Les collaborateurs reçoivent à titre d'honoraires 50 tirés-à-part gratuitement. Les tirages à part supplémentaires seront facturés à un prix spécial. La maison d'édition se charge des frais de clichés à condition qu'elle reçoive les dessins originaux se prêtant à la reproduction et que leur nombre ne dépasse pas la mesure strictement nécessaire. Dans le cas contraire les frais sont à la charge de l'auteur. Celui-ci sera avisé auparavant du montant approximatif.

Tous les articles originaux se rapportant à l'étude de la généalogie humaine peuvent être publiés dans «Acta Genetica et Statistica Medica». Les manuscrits sont acceptés dans les langues française, anglaise et allemande, et devront tous, sans exception, être suivis d'un bref résumé dans les trois langues. Les auteurs sont priés de rédiger leurs travaux aussi concis que possible; les ouvrages ne doivent pas, sauf cas exceptionnels, dépasser 10 pages imprimées.

Tous les manuscrits doivent être adressés à l'Institut Universitaire de Génétique Humaine, Tagensvej 14, Copenhague N. (Danemark). Les épreuves corrigées, les ouvrages à analyser, de même que toute correspondance concernant les abonnements et la publicité sont à adresser à la maison S. KARGER SA., Editeurs, Arnold Böcklinstrasse 25, Bâle (Suisse).

Acta genet. *11:* 97–105 (1961)

From the Zoology Department, University of Western Australia

THE DISTRIBUTION OF HAPTOGLOBIN AND TRANSFERRIN GROUPS IN SOUTH AND SOUTH EAST ASIA

By R. L. KIRK and L. Y. C. LAI

During the last few years a start has been made on plotting the world distribution of the haptoglobin and transferrin groups in Man. *Sutton, Matson, Robinson and Koucky* have recently summarized all the available surveys up to the early part of 1960. Although the populations sampled are rather patchily distributed for most of the Continental and Island peoples, and although far more attention has been given to haptoglobin than to transferrin grouping, certain significant patterns have emerged already.

In Europe the Hp^1 gene has an average frequency of 0.38 based on nearly 10,000 persons examined by different investigators with range from 0.34 to 0.46. The frequency of Hp^1 is significantly lower in Swedish Lapps (*Beckman and Mellbin*, 1959) and is only 0.30 in a small sample of Greenlanders (*Galatius-Jensen*, 1960). Persons with no definable haptoglobin group (Hp O) are rare in Europe; the frequency of Hp O is less than .005 in all samples studied except Swedish Lapps (0.02).

Reports on the frequency of the transferrin groups in Europeans are few. Approximately 1 per cent have a transferrin which migrates faster than the common Tf C band in starch-gel electrophoresis (*Smithies and Hiller*, 1959, *Harris et al.*, 1959). These faster moving variants are termed B_0, B_1 and B_2 in order of decreasing mobility, and all three have been reported in the European samples. But no case has been reported so far of a European person with one of the transferrin bands which migrate more slowly than the Tf C band, i.e., the D_0, D_1, D_2 or D_3 variants (*Giblett, Hickman and Smithies*, 1959).

Preliminary studies of the Indian populations of the American continents suggest a cline of Hp^1 gene frequency from a relatively high value of 0.73 in Peruvian Indians (*Giblett and Best*, 1960) to 0.42 for the North Athabaskan in Alaska (*Blumberg et al.*, 1959). The Eskimos in Alaska have a value of

Hp^1 around 0.30, a value comparable to that noted above for Greenlanders. The frequency of the Hp O phenotype is again low, being less than 0.01 for all except two small inbred groups, the Anaktuvuk in Alaska and the Lacandon in South Mexico. As far as the transferrins are concerned, both B and D variants have been reported among Indians in S. Mexico and Guatemala, the frequency being rather less than 0.01 in each case (*Sutton, Matson, Robinson and Koucky*, 1960).

Populations south of the Sahara in Africa show considerable variation in the Hp^1 gene frequency. High values ranging from 0.60 to 0.87 have been reported in West Africa, somewhat lower values of 0.40 to 0.60 in the Congo, reaching the value of 0.29 among the Bushmen (*Barnicot et al.*, 1959). Many of the African populations, however, are characterized by very high frequencies of persons in whom no haptoglobin group can be detected. In the studies cited above the frequency of the Hp O phenotype ranges from 0.23 to 0.48 in West Africa, averages 0.2 in the Congo, but is only 0.02 in the Bushmen. Corresponding with this range of values for the Hp O frequency the Hp 2–1 (mod.) phenotype is found commonly in West African populations, less commonly in the Congo, and none were noted in the Bushmen. The African continent is also noteworthy for the high incidence of the slow moving transferrin variants, particularly D_1. Discovered originally in samples from Australian aborigines (*Smithies*, 1957; *Horsfall and Smithies*, 1958) it occurs in approximately 10 per cent of American Negroes (*Giblett, Hickman and Smithies*, 1959) 2.6 per cent of a sample from Gambia (*Harris*, 1958) 10 per cent of Bushmen and nearly 3 per cent of Zulus (*Barnicot et al.*, 1960). No example of a B transferrin variant has been reported in the African populations so far examined.

Outside Europe, Africa and the Americas a number of isolated studies have been made. Two investigations in Japan (*Yamaguchi et al.*, 1959; *Matsunaga and Murai*, 1960) give a mean frequency for the Hp^1 gene of 0.26 whereas values from various places in Oceania and New Guinea range from 0.50 to 0.66 (*Harris et al.*, 1959; *Blumberg*, 1959; *Douglas and Stavely*, 1960; *Bennett et al.*, 1960). Low values of the Hp^1 gene frequency have been reported previously from this laboratory for Chinese, Malays and Indians in Malaya (*Kirk et al.*, 1960) the value of 0.09 for the sample of Indians being the lowest value reported so far. Similar low values of Hp^1 have also been found in Australian aborigines, although evidence is accumulating for considerable variation in frequency among different tribes (*Kirk and Lai*, unpublished). The Hp O phenotype is either absent or infrequent in the samples referred to for Asia, Oceania, New Guinea and Australia. The B transferrin variants are also absent or rare in these places, but the D_1

variant has been found in 5 per cent of Malays and 8 per cent of Chinese in Malaya, in 10 per cent of persons from the Eastern Highlands of New Guinea (*Bennett et al.*, 1960) and in nearly 50 per cent of some groups of Australian aborigines from the Western Desert (*Kirk and Lai*, unpublished).

Present Investigations

In view of these differences in the distribution of both the haptoglobin and transferrin groups in various parts of the world it became obvious that South and South-east Asia would be an important area for further study. Here people of Caucasian origin on the one hand and of Mongoloid origin on the other have penetrated into areas where a wide variety of peoples, including those of Veddoid and Negrito type had previously been established. Even the Mongoloid penetration has not been uniform and pockets of aboriginal groups of Mongoloid type are still in existance, and mixture with such groups and others during the historical period have produced regional differences in the existing modern populations.

Table I gives the haptoglobin and transferrin group distributions for 2,000 persons from a number of ethnic groups in different parts of S. and S.E. Asia. The techniques employed in collecting the samples and determining the Hp and Tf phenotypes were esentially the same as those described previously (*Kirk et al.*, 1960) with the exception that the vertical starch-gel technique was used throughout. The Hp^1 gene frequency has been determined by direct gene counting and omitting the Hp O phenotypes from the calculation. A similar method has been used to determine the Tf C gene frequency, making the assumption that the genes controlling the B and D variants are allelic.

Although there are considerable variations in both haptoglobin and transferrin frequencies between the populations sampled some generalizations emerge from a detailed consideration of the results. The whole area is characterized by a low Hp^1 gene frequency, only two groups reaching a value characteristic of European populations. On the other hand the frequency of persons with the Hp O phenotype is above that for European populations. The overall frequency is 2.4% but the range is from 0 out of 46 Tamils in Ceylon, less than 1 per cent in Bangkok Thais, to nearly 10 per cent in a sample of 66 proto-Malays. Many of these populations are from areas where malaria is endemic, and the Hp O phenotype may simply represent transient ahaptoglobinaemia resulting from haemolytic episodes. The view that the Hp O types are mainly environmental in origin in these samples is supported by the almost complete absence of the Hp 2–1 (mod.) phenotype. Only 2

examples were detected in the 2,000 sera tested. This marks out these Asian populations quite distinctly from populations in Africa, where both the Hp O and Hp 2–1 (mod.) phenotypes are relatively high.

Table I

Haptoglobin and transferrin group frequencies in various populations of South and South-East Asia

Country and Population	No. Tested	Haptoglobin groups 0	1–1	2–1	2–2	Hp^1 Frequency	Transferrin groups BC	CD_1	D_1D_1	Tf C Frequency
Ceylon										
Tamils	46	0	0	13	33	0.14	0	0	0	1.000
Singhalese	87	2	0	28	57	0.16	0	1	0	0.994
Veddahs	64	4	1	14	45	0.19	0	6	1	0.921
South India										
Tamils[1]	133	4	4	14[2]	111	0.09	0	0	0	1.000
Todas	89	1	13	36	39	0.37	0	0	0	1.000
Irulas	74	5	0	10	59	0.07	0	0	0	1.000
Kurumbas	49	1	2	13	33	0.19	0	0	0	1.000
North India										
Oraons	125	1	2	32	90	0.15	0	8	0	0.968
West Pakistan										
Punjabis	207	7	12	52	130	0.20	0	0	0	1.000
Pathans	185	5	10	67	103	0.24	2	0	0	0.995
Thailand										
Bangkok Thais	274	2	13	97	162	0.23	0	15	1	0.971
Northern Thais	139	3	7	58	71	0.26	0	15[3]	0	0.946
Maeo	34	0	3	8	23	0.21	0	1	0	0.985
Yaeo	25	3	2	4	16	0.19	0	2	0	0.960
Malaya										
Malays	236	2	12	85[2]	137	0.23	0	11	0	0.977
Chinese	167	2	18	57	90	0.28	0	7	1	0.956[4]
Proto-Malays	66	6	12	32	16	0.47	0	2	0	0.985

[1] Sampled in Malaya, but born in South India.
[2] Includes 1 Hp 2–1 (mod.) phenotype.
[3] Includes 1 CD_0 phenotype.
[4] Transferrin results of Chinese based on 103 samples only.

The distribution of the transferrin variants reveals almost a complete absence of the B types. Only two examples were detected, one B_1C and one B_2C, both in Pathans from the Peshawar area in West Pakistan. Transferrin D variants were found, however, in the Mongoloid populations or those such as the Oraons in India which have been subject to mongoloid influence. Transferrin D occurred in 3.5 per cent of all the persons tested, all but one of these being either CD_1, or D_1D_1. The one exception, a Thai from the northern provinces, was typed as CD_0.

If the present data is combined with that already in existence for Japan, Oceania, New Guinea and Australia, to which reference has been made above, certain patterns in the distribution of the haptoglobin and transferrin groups in the whole of this area become evident. Map I shows in diagramatic form the distribution of the Hp^1 and Hp^2 genes. The Indian sub-continent is an area of consistently low Hp^1 values, and there is no significant difference between the Tamils, Singhalese or Veddahs in Ceylon, or the Tamils and the veddoid Irula and Kurumba tribes in South India, or the Oraons in N.E. India. To the North West there is a slight increase in

Map 1

The distribution of the haptoglobin genes Hp^1 and Hp^2 in South and South East Asia and the Pacific Ocean.

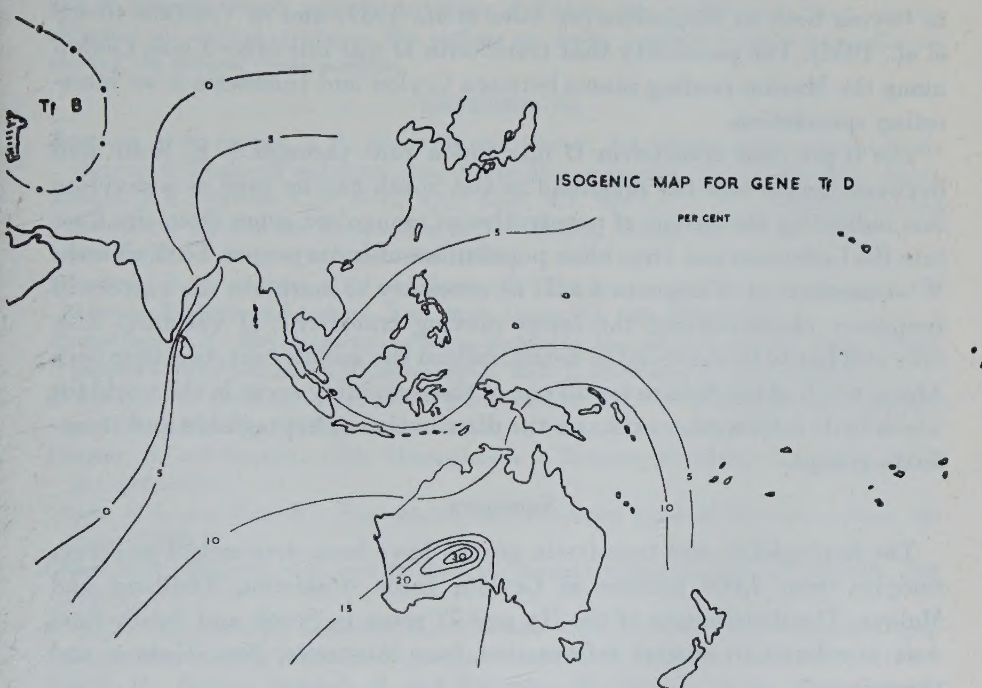
Hp^1 frequency, the value rising to 0.24 among the Pathans. This is closely similar to the value of 0.25 for a small sample of Iranians studied by *Harris et al.* (1959). The only striking exception in India is the value for Hp^1 of 0.37 for a group of Todas. The Todas of the Nilgiri Hills are a small group, numbering only 630 at the last census, and their population has been even lower earlier in the century. They are quite distinct physically and culturally from the surrounding South Indian peoples (*Rivers*, 1906), and their discrepant haptoglobin distribution may reflect a remote origin, genetic drift, or a combination of both. Other examples of significant differences between the haptoglobin gene frequencies in small inbred communities and the surrounding populations have been noted by other investigators particularly the Anaktuvuk in Alaska (*Blumberg et al.*, 1959) and the Lacandon Indians in Central America (*Sutton et al.*, 1960).

In contrast to the Indian sub-continent, the Mongoloid populations of the East and S. E. Asian continent are characterized by slightly higher Hp^1 gene frequency, ranging between 0.23 and 0.28. For convenience the Chinese sample is shown in Map I in the centre of the area of the dialects spoken by the persons sampled, although the samples were all collected from Chinese at present resident in Malaya. The aboriginal mongoloid tribes in N. Thailand, the Maeo and Yaeo, have a Hp^1 gene frequency close to 0.20, but the number sampled is small and the differences between them and the other mongoloid populations in this respect is non-significant. In contrast, the small group of 66 proto-Malays sampled in Malaya has a significantly higher Hp^1 frequency than either the Chinese of Malay populations in Malaya. It is interesting to speculate that this higher value represents part of a cline of steadily increasing Hp^1 values as one moves from the Asiatic mainland through the Indonesian Islands to Micronesia and Polynesia. The high Hp^1 value in New Guinea is consistent with this trend, although quite clearly more detailed studies will be required to substantiate it.

Finally, aboriginal Australia appears to be an area of relatively low Hp^1 values as far as present investigations using starch-gel electrophoresis permit generalizations concerning the continent as a whole. The higher values reported for Central and North East Australia reported by *Budtz-Olsen* (1958) using paper electrophoresis still await confirmation.

Map 2 represents a preliminary attempt to plot the isogenic contours for the transferrin gene Tf D. The highest known frequency of Tf D occurs among aborigines in the Western Desert. A value of 0.32 has been obtained for a sample of 190 persons from Yalata in South Australia (*Bennett and Cooper*, personal communication). At the Western end of this area the Tf D gene is somewhat lower, with a value of 0.22 (*Kirk and Lai*, unpublished

observations). In North Western Australia the Tf D value is considerably lower at 0.08 (*Kirk and Lai*, unpublished observations). Figures elsewhere in Australia are not yet available, but the preliminary publication of *Horsfall and Smithies* (1958) is suggestive of a reasonably high value of Tf D, though it is not possible to calculate it accurately from the published information.



Map 2

Isogenes for transferrin D in South and South East Asia and the Pacific Ocean.

Outside Australia the Tf D gene is common in the Eastern Highlands of New Guinea, having a value of 0.11 (*Bennett et al.*, 1960). Eastwards the frequency falls away rapidly and is zero in 200 Tongans and 82 Samoans that have been tested (*Staveley*, personal communication).

In Asia the transferrin D variants are confined mainly to the mongoloid populations. It is absent from the mainland of India and Pakistan, except for the Oraons in the North East. Since these people also have a small percentage of Diego +ve individuals it suggests that Mongoloid genes may have penetrated into these fringe areas (*Vos and Kirk*, 1960). The Tf D gene has found its way also into Ceylon, where it achieves a frequency of 0.08 in

the Veddahs. This raises an important problem. The complete absence of the Tf D gene in South India, despite the supposed relationship between the veddoid tribes of South India and the Veddahs of Ceylon, suggests that the D gene has gained entry to Ceylon in relatively recent times. Evidence in support of this is to be found in the fact that although haemoglobin S is common in the veddoid populations of South India, haemoglobin E is found in Ceylon both in Singhalese (*de Silva et al.*, 1959) and in Veddahs (*Graff et al.*, 1955). The possibility that transferrin D was introduced into Ceylon along the Muslim trading routes between Ceylon and Indonesia is an interesting speculation.

The 0 per cent transferrin D line which runs through N.E. India and between Ceylon and the mainland in the South can be used as a dividing line indicating the extent of penetration of mongoloid genes from the East into the Caucasian and Dravidian populations of India proper. To the North-West another set of isogenes would be necessary to mark out the pattern of frequency characterizing the faster moving transferrin B variants. This area still has to be surveyed in detail. Indeed the middle east, together with Africa north of the Sahara is still one of the remaining areas in the world for which little information exists on the distribution of haptoglobin and transferrin groups.

Summary

The haptoglobin and transferrin groups have been determined in serum samples from 2,000 persons in Ceylon, India, Pakistan, Thailand and Malaya. The distribution of the Hp and Tf genes in South and South-East Asia is related to similar information from Australia, New Guinea and Oceania.

Zusammenfassung

Im Serum von 2000 Personen aus Ceylon, Indien, Pakistan, Thailand und Malaya wurden die Haptoglobin- und Transferrin-Gruppen bestimmt. Die Verteilung der Hp- und Tf-Gene in Süd- und Südost-Asien wurde zu entsprechenden Daten aus Australien, Neuguinea und Ozeanien in Beziehung gesetzt.

Résumé

Les groupes d'haptoglobuline et de transferrine ont été déterminés dans le sérum de 2000 personnes de Ceylan, de l'Inde, du Pakistan, de Thaïlande et de Malaya. La distribution des Hp et de Tf gènes dans le Sud et le Sud-Est de l'Asie correspond à des informations analogues provenant d'Australie, de la Nouvelle-Guinée et d'Océanie.

Acknowledgements

Generous financial assistance was provided by the University of Western Australia and the Australian National Health and Medical Research Council.

One of us *(R.L.K.)* received a fellowship from the South East Asian Treaty Organization which made possible the collection of the samples in Ceylon, India, Pakistan and Thailand. In these countries and in Malaya valuable assistance was given by Drs. *R.L. Wickremasinghe*, *T.E. Perera*, *Ali Mohammed Khan*, *Sommai Sri-Ngarm*, *Syed Mahmood* and *R. Bhagwan Singh*, and also by Sister *D. Piljain*. Mrs. *Dell Vos* rendered valuable technical and clerical assistance. The authors are deeply indebted to all these persons for making the present study possible.

REFERENCES

Barnicot, N.A.; Garlick, J.P.; Singer, R. and Weiner, J.S.: Haptoglobin and transferrin variants in Bushmen and some other South African peoples. Nature *184:* 2042 (1959).

Bennett, J.H.; Auricht, C.O.; Gray, A.J.; Kirk, R.L. and Lai, L.Y.C.: Haptoglobin and transferrin types in the Kuru region of New Guinea. Nature *189:* 68–69 (1961).

Blumberg, B.S.: Quoted in *Sutton et al* (1960).

Blumberg, B.S.; Allison, A.C. and Garry, B.: The haptoglobins and haemoglobins of Alaskan Eskimos and Indians. Ann. hum. Genet. *23:* 349–356 (1959).

Budtz-Olsen, O.E.: Haptoglobins and haemoglobins in Australian aborigines, with a simple method for the estimation of haptoglobins. Med. J. Australia, *ii:* 689–692 (1958).

de Silva, C.C.; Jonxis, J.H.P. and Wickremasinghe, R.L.: in Abnormal Haemoglobins, pp. 340–357 (Oxford 1959).

Douglas, R. and Staveley, J.M.: Haptoglobins in Tongans (Polynesia) N. Z. Med. J. *ii:* 391–392 (1960).

Giblett, E.R. and Best, W.: Haptoglobin and transferrin types of Peruvian natives. (In press.) (1960.)

Giblett, E.R.; Hickman, C.G. and Smithies, O.: Serum transferrins. Nature *183:* 1589–1590 (1959).

Graff, J.A.E.; Ikin, E.; Lehmann, H.; Mourant, A.E.; Parkin, D. and Wickremasinghe, R.L.: Haemoglobin E and blood groups in Veddahs. J. Physiol. (Lond.) *127:* 41 (1955).

Harris, H.; Robson, Elizabeth, B. and Siniscalco, M.: Genetics of the plasma protein variants. In Biochemistry of Human Genetics. CIBA Found. Symp. (London 1959).

Horsfall, W.R. and Smithies, O.: Genetic control of some human serum β-globulins. Science *128:* 35 (1958).

Kirk, R.L.; Lai, L.Y.C.; Mahmood, S. and Singh, R. Bhagwan: Haptoglobin types in S. E. Asia. Nature *185:* 185–186 (1960).

Rivers, W.H.R.: The Todas (London 1906).

Matsunaga, E. and Murai, K.: Haptoglobin types in a Japanese population. Nature *186:* 320–321 (1960).

Smithies, O.: Variations in human serum β-globulins. Nature *180:* 1482–1483 (1957).

Smithies, O. and Hiller, O.: The genetic control of transferrins in humans. Biochem. J. *72:* 121–126 (1959).

Sutton, H.E.; Matson, G.A.; Robinson, A.R. and Koucky, R.W.: Distribution of haptoglobin, transferrin and hemoglobin types among Indians of Southern Mexico and Guatemala. Amer. J. hum. Genet. *12:* 338–347 (1960).

Yamaguchi, M.; Yanase, T. and Kawamura, K.: Quoted in *Sutton et al.* (1960).

Authors' address: Dr. R. L. Kirk and Dr. L. Y. C. Lai, Zoology Dept., Univ. of Western Australia, Nedlands (Australia)

Acta genet. *11:* 106–110 (1961)

From the Institute for Medical Genetics, Uppsala

TRANSFERRIN VARIANTS IN LAPPS AND SWEDES

By LARS BECKMAN and GÖSTA HOLMGREN

1. Introduction

By means of starch gel electrophoresis *Smithies* (1957) observed a slowly migrating β-globulin component (termed β-globulin D), which occurred together with the normal β-globulin component in human serum (β-globulin C). The two components occurred in about equivalent amounts and were found in the sera of 2 out of 49 New York negroes and 5 out of 23 Australian aborigines studied. A fast moving β-globulin variant (B) was observed by *Smithies* (1958) in 4 Canadian whites (out of 425 studied). Family data by *Horsfall and Smithies* (1958) and *Smithies and Hiller* (1958) indicate that the β-globulins B, C and D are genetically controlled by three autosomal alleles. *Giblett, Hickman and Smithies* (1959) concluded from experiments with radioactive iron that the variable β-globulins were ironbinding proteins (transferrins). Further there are four different transferrin components moving more slowly than the ordinary transferrin C (D_0, D_1, D_2 and D_3) and three different components moving faster than transferrin C (B_0, B_1 and B_2). B_0 is the fastest and D_3 the slowest transferrin (*Harris et al.*, 1959).

The symbol Tf has been suggested for the locus and the main alleles are termed Tf^B, Tf^C and Tf^D (adding together the different B- and D-variants). The normal genotype is thus designated TfCC. The frequency of TfB_2C in Canadian whites and Englishmen is about 1 per cent, while the $TfCD_1$ phenotype is rather common (about 10 per cent) in Negroes and Australian aborigines (*Harris et al.*, 1959). Fast transferrins (B) have so far not been observed in Negroes and Australian aborigines and slow transferrins have not been reported in whites. A transferrin polymorphism similar to that found in human sera has been described also in monkeys (*Blumberg*, 1960; *Beckman, Hirschfeld and Söderberg*, 1960).

2. This investigation

The sera of the Lapp series have been collected from children attending the nomad schools of the county of Norrbotten. Most of the 329 children are true nomad Lapps. Blood groups (*Beckman, Broman, Jonsson and Mellbin*, 1959) and haptoglobin groups (*Beckman and Mellbin*, 1959) of the same series have been reported previously.

The sera of 450 Swedes were collected from blood donors in four different localities in North Sweden.

The sera were examined by starch gel electrophoresis using the discontinuous buffer system by *Poulik* (1957) and a modified buffer system suggested by Dr. *G. C. Ashton* (personal communication). This system consists of two buffers: (1) 1.2 g Lithium hydroxide + 11.89 g Boric acid/1 litre and (2) 1.6 g Citric acid + 6.29 g Tris Sigma 121/1 litre. Buffer (1) is used in the electrode vessels and for the gels a mixture of 10 per cent of buffer (1) and 90 per cent of buffer (2) is used. This system gives a good resolution especially in the region between the β-globulins and the albumin.

The ironbinding capacity of the transferrin bands was demonstrated by means of radioactive iron (^{59}Fe), which was added to the sera prior to the electrophoresis. The gels were stained with amidoblack and sectioned into pieces of the same width as the transferrin bands. The pieces were then put into test tubes and the radioactivity measured in a scintillation counter. The pieces containing the transferrin bands showed a clearly increased activity as compared to pieces from other parts of the gel. This method is simple and rapid and when the purpose is to show only the ironbinding capacity, and not to make quantitative measurements, it may be accurate enough.

Table 1

Blood groups and haptoglobin groups of six Swedish Lapps with $TfCD_1$

Individual	Hp	Blood groups				
		ABO	MN	Rh	P	Kell
1	2–2	A_2	N	CcDE	P—	K—
2	2–2	A_2	MN	CcDE	P—	K—
3	2–2	A_2	N	D	P+	K—
4	no haptoglobin	0	M	CCD	P—	K—
5	2–1	A_2B	MN	C^WcD	P—	K—
6	2–1	A_2	MN	C^WcD	P—	K—

No. 1–2 and 5–6 are sibs.

In six of the 329 Lapp individuals (about 2 per cent) a slow transferrin band was found in addition to transferrin C. All heterozygotes were of the same type and a double run together with a reference serum revealed that the type was $TfCD_1$. Blood groups and haptoglobin groups of the individuals with this transferrin type are shown in table 1. In spite of the small numbers one may note that five individuals possess the A_2-gene, one individual lacks detectable haptoglobin pattern and two individuals have the C^W-gene, which is rare in Europeans.

Five of the 450 blood donors showed fast transferrin components (cf. fig. 1). Four individuals were TfB_2C and one had the type TfB_1C. Thus the transferrins of the Swedish sample agrees with earlier results from white people. Four of the five transferrin heterozygotes were found in a sample of one hundred individuals from Dalecarlia. This indicates that regional variations may exist in Sweden.

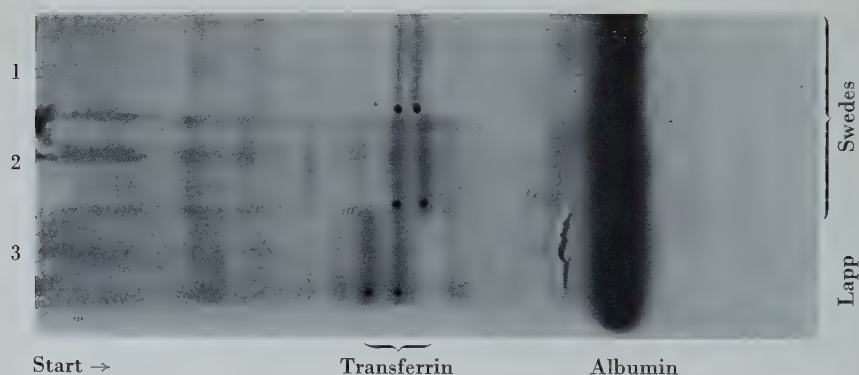


Fig. 1. Photograph of a starch gel showing the transferrin patterns of three different sera examined on the same gel. 1 and 2 are two different heterozygous types with two different fast components (found in the Swedish sample), 3 is a heterozygote with a slow component (found in the Lapp sample). The transferrin components are indicated by black dots.

3. *Discussion*

As previously mentioned fast transferrin variants have been found only in Caucasians and slow ones only in Australian aborigines and African race groups. Our finding of a slow transferrin variant in the Lapps shows that this anthropological distinction does not hold true any longer. It might be questioned if the slow transferrin of the Lapps really represents the same mutation as the TfD_1. It seems very probable, however, it is the transferrin type CD_1. The next problem then is what kind of anthropological informa-

tion may be extracted from the present observation. The Lapps represent, undoubtedly, a Caucasian group, although distinct from all other populations so far studied. All anthropological comparisons with Negroes and Australians seem quite absurd. It is therefore highly desirable that caution should be exercised in drawing conclusions concerning the relationships between different ethnic groups, based on population studies of transferrin variants, until more extensive studies of the distribution of transferrins have been performed.

Summary

The transferrin variants of 329 Swedish nomad Lapp children and 450 Swedish blood donors from northern Sweden have been examined. Six of the Lapps had slow transferrin variants and five of the Swedes had fast transferrin variants.

Zusammenfassung

Die Transferrin-Gruppen von 329 Kindern nomadisierender Lappen aus Schweden sowie 450 schwedischen Blutspendern aus Nordschweden wurden untersucht. Bei 6 Lappen zeigten sich langsame, bei 5 Schweden rasche Transferrinvarianten.

Résumé

Les variations de la transferrine ont été examinées chez 329 enfants lapons nomades suédois et 450 donneurs de sang suédois du nord de la Suède. Chez six des Lapons, on a trouvé des variantes lentes de la transferrine et cinq Suédois avaient des variantes rapides de la transferrine.

ACKNOWLEDGEMENT

Our thanks are due to Dr. Eloise *R. Giblett*, King County Central Blood Bank, Seattle, for supplying us with the reference sera used in this investigation.

LITERATURE

Beckman, L.; Broman, B.; Jonsson, B. and Mellbin, T.: Further data on the blood groups of the Swedish Lapps. Acta genet. *9:* 1–8 (1959).

Beckman, L. and Mellbin, T.: Haptoglobin types in the Swedish Lapps. Acta genet. *9:* 306–309 (1959).

Beckman, L.; Hirschfeld, J. and Söderberg, U.: Transferrin variations in sera of Macaca irus. Acta path. microbiol. scand. (in press).

Blumberg, B.S.: Biochemical polymorphisms in animals: haptoglobins and transferrins. Proc. Soc. exp. Biol., N.Y. *104:* 25–28 (1960).

Giblett, E.R.; Hickman, C.G. and Smithies, O.: Serum transferrins. Nature, London *183:* 1589–1590 (1959).

Harris, H.; Robson, E.B. and Siniscalco, M.: Genetics of the plasma protein variants. Ciba Found. Symp. Biochemistry of Human Genetics, pp. 151–177 (Churchill, London 1959).

Horsfall, W.R. and Smithies, O.: Genetic control of some human serum β-globulins. Science *128:* 35 (1958).

Poulik, M.D.: Starch gel electrophoresis in a discontinous system of buffers. Nature, London *180:* 1477–1479 (1957).

Smithies, O.: Variations in human serum β-globulins. Nature, London *180:* 1482–1483 (1957). – Third allele at the serum β-globulin locus in humans. Nature, London *181:* 1203–1204 (1958).

Smithies, O. and Hiller, O.: The genetic control of transferrins in humans. Biochem. J. *72:* 121–126 (1958).

Authors' addresses: Dr. Lars Beckman and Dr. Gösta Holmgren, Institutionen för Medicinsk Genetik, 24 V. Ågatan, *Uppsala* (Sweden).

Acta genet. *11:* 111–125 (1961)

From the University Institute of Human Genetics, Oslo

ON THE GENETICS OF THE Gm SERUM SYSTEM

By BRITA BRANDTZÆG and JAN MOHR

Introduction

Since *Grubb and Laurell* (1956) discovered the Gm serum system, their hypothesis on its basic structure has been confirmed by several workers (notably *Moullec et al.*, 1956; *Linnet-Jepsen, Galatius-Jensen and Hauge*, 1958; *Mäkelä and Tiilikainen*, 1959; *Harboe and Lundevall*, 1959). New traits have at the same time been discovered, so that in becoming more accurate, our picture of the system has also grown more complex.

The following outline seems to be in accordance with the data available at present:

Besides a basic dichotomy represented by two allelic genes Gm^a and Gm^b, of which the former (*Grubb and Laurell*, 1960) as well as the latter (*Harboe*, 1959) are positively diagnosable by specific antisera, there is a differentiation into subtypes.

Of these only one has yet been studied to any extent, namely that given by the serum provisionally designated anti-Gm(x). The factor Gm^x was discovered by *Harboe and Lundevall* (1959), and examined in sera from unrelated individuals provided by these workers, as well as in a family material collected by the present writers. In this material Gm(x) was diagnosed in nearly half of individuals possessing Gm(a), and exclusively in such individuals. The serum anti-Gm(x) thus appeared to give a differentiation of Gm(a) into two subtypes, analogous to the differentiation of A in the A_1A_2BO blood group system into the subtypes A_1 and A_2. Accordingly the terms a_1 and a_2 were proposed for the subtypes of a in the Gm system (*Grubb*, 1959). *Henningsen* (1960, personal communication) has, however, diagnosed Gm(x) in an individual who appears not to possess Gm(a). Thus the dependency of Gm(x) on Gm(a) may be spurious, except in a statistical manner, and the analogy with the A_1A_2BO system misleading.

Another differentiation of Gm(a), discovered by *Fudenberg* (1960, personal communication), is given by a serum with the preliminary designation

anti-Gm(r). According to *Fudenberg* the factor Gm(r) is present in about ninety per cent of individuals possessing Gm(a), and, so far the observations go, only in such individuals. Concerning the relation between Gm(r) and Gm(x), Gm(x) appears to be dependent upon Gm(r) in the sense that it rarely, if at all, occurs in individuals lacking Gm(r) (own observations, unpublished).

The relation between Gm(a), Gm(r) and Gm(x) may, in other words, be so described: Gm(r) is, at least in a statistical sense, a subfactor of Gm(a), and Gm(x) is similarly a subfactor of Gm(r).

While the factors mentioned above are interrelated in a way indicating that they are parts of the same genetical system, the genetic relationship, if any, to the Gm-system, of the so-called Gm-like factor discovered by *Steinberg* (1960), is not yet clear. This factor, which is common in Negroes, but not yet observed in Whites, is diagnosed by a system similar to that used to detect Gm(a). It is, like the other factors, inherited as a dominant.

Puzzling observations have been made on Negroes (*Steinberg*, personal communication), that may be interpreted to mean that Gm^a and Gm^b is, in Negroes, frequently present in the same chromosome. One should, however, be cautious in interpreting this as evidence against the hypothesis that Gm^a and Gm^b are allelomorphs; the results obtained on Negroes and Whites by the same testing system, may not, offhand, be considered strictly comparable.

Notation. Phenotypes are written Gm(abx), Gm(a$\bar{b}$x), Gm(a$\bar{b}\bar{x}$), Gm($\bar{a}$b$\bar{x}$), Gm(ab$\bar{x}$), where an unmarked letter denotes the presence of the factor concerned, a letter marked with a bar, its absence. ($\bar{x}$ is read x−, x is read x+, etc.)

The justification for adopting in the present paper this a bit unusual way of writing phenotypes, may be questioned. This more concise notation for phenotypes, however, gives the special advantage in the present case, where the testing is done by an inhibition reaction, of giving different symbols for the primary readings (where + means no inhibition) and the final test result (where no inhibition means absence of the factor concerned). Besides, the transformation from traditional notation is, in fact, slight, reversion to traditional writing being attained, by those who so desire, by simply writing a as a+ and $\bar{a}$ as a—, etc.

It may further be questioned whether it is justifiable to maintain the symbol x, which, besides appearing more appropriate for preliminary use within a laboratory than as a permanent designation, breaks with the generally accepted rule that neighbouring letters should be used for genes which belong to the same system. In a not preliminary notation for the Gm

system symbols like x ought perhaps to be replaced by more instructive terms, if not too firmly established by tradition.

Purpose of the present study. The purpose of this paper is to examine the question of how far the data at present available support the genetic conceptions discussed above, and how "useful" the system may be in human genetics. In particular the following points are considered:

1. If individuals of Gm-types other than those compatible with the hypothesis exist, such as for instance Gm($\bar{a}\,\bar{b}\,\bar{x}$) individuals, how rarely may these be assumed to occur?
2. On the assumption that exceptions from the postulated mode of transmission occur, for instance Gm(a) children in Gm($\bar{a}$) $\times$ Gm($\bar{a}$) marriages, how rare may these be assumed to be?
3. Is there any evidence of deviation from panmixia, such as deviating segregation ratios or assortive mating?
4. How efficient may the Gm-system be as a chromosome marker in studies of identity, zygosity of twins, parentage, linkage, etc.?
5. What indications of variation between populations in gene frequencies are given by the data considered here?

Material

The material tested by the authors comprises 199 unrelated individuals and 28 families with 83 children. In addition 24 normal families with 66 children are considered; these are included among 33 normal families collected earlier by the authors, and kindly typed for the Gm-system by *Harboe and Lundevall* (*Harboe and Lundevall*, 1959; *Harboe*, 1959).

Out of the 199 unrelated individuals, 125 are patients from Radiumhospitalet, Oslo, whereof there are 100 with uterine cancer, 25 with breast cancer; 58 are from families with sphaerocytosis, some of them being patients; the remaining 16 are random, normal individuals. All are adults.

The 28 families with 83 children, typed by the authors, were selected on the basis of the occurrence of sphaerocytosis in the kindred of the family, a study of sphaerocytosis being the main purpose.

Methods

The sera were collected from the earlobe by making a small incision with a bit of a razor blade, about 1 ml. of full blood being collected from each person.

The tests were carried out according to the agglutination-inhibiton procedure devised by *Grubb and Laurell* (1956), largely as modified by

Harboe and Lundevall (1959). (As will be known to most readers, the sera are, in this procedure, typed by their inhibitory – or non-inhibitory – action on an indicator system, which consists of a specific "antibody" and red cells coated with the corresponding "antigen").

As, in our case, it was difficult to secure the appropriate fresh cells at all times, frozen cells were tried. The reactions were not found noticeably different with these, and frozen cells were therefore used throughout. Cells from a single person of type O, Rh (C+D+E—c—) were used for all tests.

In the Gm(a) and Gm(x) testing the red cells were coated with the incomplete anti-D serum R.A., kindly supplied by Dr. *O. Hartmann*, Statens Institutt for Folkehelse, Oslo, the same as was used by *Harboe and Lundevall* (1959) for this testing. In the Gm(b) testing the red cells were coated with the incomplete anti-D serum S.V., also supplied by Dr. *Hartmann* and the same as was used by *Harboe* (1959) for this testing. At first another incomplete anti-D serum, kindly supplied by Dr. *A.G. Steinberg*, Western Reserve University, Ohio, was tried. Since equally good results were obtained with S.V., which was available in Oslo, this serum was chosen for the routine testing.

Coating of the cells was carried out by first washing them four times in saline, then adding one volume of packed cells to one volume of anti-D. In the case both of R.A. and S.V. the dilution 1:5 was found appropriate. After incubation at 37° C for about 1 hour, the cells were washed 4 times in saline, and a suspension of approximately 0.3% was prepared.

Two different anti-Gm(a) sera were used during the study. In the sphaerocytosis families, 177 individuals were tested with the serum anti-Gm(a) E.K., kindly supplied by *Harboe and Lundevall*, (1959), the remaining 48 individuals with anti-Gm(a) K.K., a serum found by the authors in a patient with sphaerocytosis. (Tests for specificity of this serum included examination of 100 individuals of the family material, half of which had earlier been found to be Gm(a) and half Gm($\overline{a}$), with anti-Gm(a) E.K., the results with the new serum being identical with the former). The unrelated individuals, except those included in the family material, were all tested with anti-Gm(a) K.K.

For the Gm(x) typing the anti-Gm(x) M.S., supplied by *Harboe and Lundevall*, was used throughout.

The Gm(b) typing was made by anti-Gm(b) Bomb., kindly provided by Dr. *A.G. Steinberg*, Western Reserve University, Ohio.

In all tests the anti-serum was used in three dilutions, 1:8, 1:16, and 1:32 while the normal serum to be tested was always diluted 1:8.

Equal volumes of anti-serum, normal serum and suspension of coated cells were used, the sera being mixed first and the cells added afterwards.

It was found convenient to measure off the volumes by means of a 5 mm³ "Carlsberg-pipette", thereby securing economy with test-sera, as well as greater accuracy and convenience in testing.

The tests were carried out on large glass slides kept in a moist chamber, each slide carrying ten tests. The chamber with the slides was placed on a shaking machine producing a slight circular motion. With this machine and the small volumes applied, it was not found necessary to use paraffin rings to keep the reagents in place, as recommended by *Harboe and Lundevall* (1959). The slides were generally left 10–15 minutes on the shaking machine and afterwards allowed to stand at room temperature for about 15 minutes, the exact time applied in each case being determined by the state of the controls. Positive and negative controls were always included.

In the great majority of cases clear-cut reactions were obtained. In a few doubtful cases repeated tests were carried out, without in any case recognizing any true intermediate.

Results and analysis

The distribution of the 199 unrelated individuals on the eight possible combinations given by the three dichotomies defined by the three sera anti-

Table 1

Distribution of 199 unrelated Norwegian individuals on the phenotypes given by anti-Gm(a), anti-Gm(x), and anti-Gm(b)

	Gm(a)				Gm($\bar{a}$)				
	Gm(x)		Gm($\bar{x}$)		Gm(x)		Gm($\bar{x}$)		
	Gm(b)	Gm($\bar{b}$)	Gm(b)	Gm($\bar{b}$)	Gm(b)	Gm($\bar{b}$)	Gm(b)	Gm($\bar{b}$)	Total
Patients with uterine cancer	18 (17.38)	8 (8.40)	33 (29.38)	1 (5.48)			40 (39.36)		100
Patients with breast cancer	5 (4.34)	3 (2.10)	7 (7.34)	0 (1.38)			10 (9.84)		25
Normal random individuals	1 (2.78)	0 (1.32)	5 (4.71)	4 (0.88)			6 (6.31)		16
Non-related individuals from families with sphaerocytosis	12 (10.08)	7 (4.87)	15 (17.04)	2 (3.18)			22 (22.83)		58
Total	36 (34.58)	18 (16.69)	60 (58.47)	7 (10.92)			78 (78.34)		199

Gm(a), anti-Gm(x), and anti-Gm(b) is shown in table 1. The expected numbers are given in brackets, calculated on the assumption of panmixia, and applying the gene frequencies Gm^x: 0.1385, Gm^a: 0.3726, Gm^b: 0.6274; these frequencies are the ones found in Norwegians by *Harboe and Lundevall* (1959), and *Harboe* (1959).

The distribution of mating types in the sphaerocytosis families is shown in table 2. The numbers expected on the assumption of random mating, given the observed distribution of mothers and fathers, are shown in brackets. Although the smallness of the numbers only permits detection of great deviations from random mating, the tabulation was considered to have interest, partly because it makes possible the easy combination of the present data with those of future workers.

Table 2

Mating types in 52 sphaerocytosis families

father \ mother			Gm(a)				Gm($\overline{a}$)	
			Gm(x)		Gm($\overline{x}$)		Gm($\overline{x}$)	
			Gm(b)	Gm($\overline{b}$)	Gm(b)	Gm($\overline{b}$)	Gm(b)	
Gm(a)	Gm(x)	Gm(b)	3 (3.00)	3 (2.00)	1 (2.25)	1 (1.00)	5 (4.75)	13
		Gm($\overline{b}$)	0 (0.69)	1 (0.46)	1 (0.52)	0 (0.23)	1 (1.09)	3
	Gm($\overline{x}$)	Gm(b)	6 (3.69)	1 (2.46)	4 (2.77)	1 (1.23)	4 (5.84)	16
		Gm($\overline{b}$)	0 (0.69)	1 (0.46)	0 (0.52)	1 (0.23)	1 (1.09)	3
Gm($\overline{a}$)	Gm($\overline{x}$)	Gm(b)	3 (3.92)	2 (2.76)	3 (2.94)	1 (1.31)	8 (6.21)	17
			12	8	9	4	19	52

In table 3 the distribution of the children in the same 28 families on the eight theoretically possible phenotype combinations is given for the various observed mating types, the expected numbers being shown in brackets. (Three empty columns are not included in the tables.) The genotypes shown in the "class of mating" column, are those which could be recognized by consideration of the parents only, disregarding the children.

In table 4 the 24 normal families have been added to those shown in table 3.

In order to consider more closely the relationship between the three factors Gm^x, Gm^a and Gm^b, the results were arranged as shown in tables 5, 6, and 7. Table 5 shows the Gm(a) and Gm(b) types for our whole material, including all the sphaerocytosis families, and the normal families typed by

Table 3

Distribution of children in 28 sphaerocytosis families tested with anti-Gm(a), anti-Gm(b), anti-Gm(x)

Class of mating			No. of fam.	No. of children	Gm(ax)	Gm^aGm^a	$Gm^{ax}Gm^b$	Gm^aGm^b	Gm^bGm^b
Gm (ax)[1]	×	Gm(ax)	1	4	4 (3.41)	0 (0.59)			
Gm (ax)	×	Gm^a Gm^b	1	2	2 (0.37)	0 (0.10)	0 (0.98)	0 (0.55)	
Gm (ax)	×	Gm^{ax} Gm^b	1	3	2 (0.39)		1 (1.67)	0 (0.94)	
Gm^a Gm^a	×	Gm^a Gm^b	1	3		1 (1.50)		2 (1.50)	
Gm^{ax} Gm^b	×	Gm^{ax} Gm^b	3	7	0 (1.75)		6 (3.50)		1 (1.75)
Gm^{ax} Gm^b	×	Gm^a Gm^b	4	16	3 (4.00)		4 (4.00)	5 (4.00)	4 (4.00)
Gm^a Gm^b	×	Gm^a Gm^b	1	4		0 (1.00)		4 (2.00)	0 (1.00)
Gm(ax)	×	Gm^b Gm^b	2	4			3 (2.56)	1 (1.44)	
Gm^a Gm^a	×	Gm^b Gm^b	1	2				2 (2.00)	
Gm^{ax} Gm^b	×	Gm^b Gm^b	4	10			8 (5.00)		2 (5.00)
Gm^a Gm^b	×	Gm^b Gm^b	5	13				8 (6.50)	5 (6.50)
Gm^b Gm^b	×	Gm^b Gm^b	4	15					15 (15.00)
			28	83	11 (9.92)	1 (3.19)	22 (17.71)	22 (18.93)	27 (33.25)

Only phenotype written in because more than one genotype is possible.

Harboe, as well as 119 unrelated individuals of *Harboe* (1959). Tables 6 and 7 show the corresponding relations for Gm(a) and Gm(x), and for Gm(x) and Gm(b); the 482 individuals comprised in these two tables are identical; these individuals are all included among the 551 individuals of table 5.

Table 4

Distribution of children in 28 sphaerocytosis families and 24 normal families tested with anti-Gm(a), anti-Gm(b), anti-Gm(x)

Class of mating		No. of fam.	No. of children	Gm(ax)	Gm^aGm^a	$Gm^{ax}Gm^b$	Gm^aGm^b	Gm^b
Gm(ax)	× Gm (ax)	2	6	6 (5.13)	0 (0.87)			
Gm(ax)	× $Gm^a Gm^a$	1	2	2 (1.56)	0 (0.44)			
Gm(ax)	× $Gm^{ax} Gm^b$	2	5	2 (0.65)		2 (2.78)	1 (1.57)	
Gm(ax)	× $Gm^a Gm^b$	2	7	3 (1.28)	2 (0.36)	0 (3.43)	2 (1.93)	
$Gm^a Gm^a$	× $Gm^a Gm^b$	1	3		1 (1.50)		2 (1.50)	
$Gm^{ax} Gm^b$	× $Gm^{ax} Gm^b$	3	7	0 (1.75)		6 (3.50)		1 (1.75
$Gm^{ax} Gm^b$	× $Gm^a Gm^b$	8	29	5 (7.25)		8 (7.25)	8 (7.25)	8 (7.25
$Gm^a Gm^b$	× $Gm^a Gm^b$	4	12		2 (3.00)		10 (6.00)	0 (3.00
Gm(ax)	× $Gm^b Gm^b$	3	6			4 (3.84)	2 (2.16)	
$Gm^a Gm^a$	× $Gm^b Gm^b$	2	5				5 (5.00)	
$Gm^{ax} Gm^b$	× $Gm^b Gm^b$	8	21			14 (10.50)		7 (10.50)
$Gm^a Gm^b$	× $Gm^b Gm^b$	8	20				12 (10.00)	8 (10.00)
$Gm^b Gm^b$	× $Gm^b Gm^b$	8	27					27 (27.00)
		52	150	18 (17.62)	5 (6.17)	34 (31.30)	42 (35.41)	51 (59.50)

Table 5

Interdependency of Gm(a) and Gm(b) types
Expected numbers on the hypothesis of independency are shown in brackets

	Gm(b)	Gm($\overline{b}$)	
Gm(a)	269 (298.33)	80 (50.67)	349
Gm($\overline{a}$)	202 (172.67)	0 (29.33)	202
	471	80	551

(Frequency of Gm($\overline{a}$ $\overline{b}$) individuals below 0.54% with 95% confidence)

Table 6

Interdependency of Gm(a) and Gm(x) types
Expected numbers on the hypothesis of independency are shown in brackets

	Gm(x)	Gm($\overline{x}$)	
Gm(a)	146 (93.29)	162 (214.71)	308
Gm($\overline{a}$)	0 (52.71)	174 (121.29)	174
	146	336	482

(Frequency of Gm($\overline{a}$ x) individuals below 0.62% with 95% confidence)

Table 7

Interdependency of Gm(x) and Gm(b) types
Expected numbers on the hypothesis of independency are shown in brackets

	Gm(b)	Gm($\overline{b}$)	
Gm($\overline{x}$)	101 (126.0)	45 (20.0)	146
Gm(x)	315 (290.0)	21 (46.0)	336
	416	66	482

(Independency χ^2 [1] = 51.75 $P < 0.001$)

Discussion

The problems in point may conveniently be discussed in the same order as they are stated in the introduction:

Occurrence of unexpected phenotypes. It appears from table 5 that not a single Gm($\bar{a}\bar{b}$) individual was observed among 551 tested persons. From this it may be stated with 95% confidence that the true frequency of such individuals does not exceed 0.54% (*Hald*, 1952).

From table 6 it appears that no Gm($\bar{a}$x) individual occurred among 482 tested individuals, whence it may be concluded with the same degree of confidence that the true frequency of such individuals does not exceed 0.62%.

Table 7, which gives the relation between Gm(x) and Gm(b), shows that none of the four possible combinations was lacking. But an antithetical relationship, in conformity with the hypothesis that these factors are allelomorphic, is apparent by a pronounced deficiency in the Gm(xb) and the Gm(x$\bar{b}$) cells.

Unexpected cases of transmission. In order to approach the question of whether exceptions from the expected manner of transmission occur, the Gm($\bar{a}$) matings were first considered. The results of the family studies of *Linnet-Jepsen, Galatius-Jensen and Hauge* (1958) [including 21 families earlier published by *Grubb* and *Laurell* (1956)], *Mäkelä and Tiilikainen* (1959), and own material are brought together in tables 8 and 9. It appears that in the 51 Gm($\bar{a}$) $\times$ Gm($\bar{a}$) families all the 146 children were Gm($\bar{a}$). Judging from this, the frequency of Gm(a) children from such matings, if occurring at all, is probably (95% confidence) below 2.03%.

As to other possible exceptions, only the results shown in table 4 could be applied, since we do not know of any other family material tested with sera other than anti-Gm(a). As it appears from the table, no individual was found in any cell with expectation zero. Considering all such possible exceptions together (ignoring the Gm($\bar{a}$) $\times$ Gm($\bar{a}$) matings, which have been already considered), the frequency of deviations from the expected mode of transmission, if occurring at all, was found to be probably (95% confidence) not above 2.40%.

Deviation from panximia. For assessment of segregation ratios, the available family material is shown in tables 8 and 9. There are in all, 274 families of mating type Gm(a) $\times$ Gm(a) or Gm(a) $\times$ Gm($\bar{a}$). When these are considered together, there is no indication of any abnormal segregation.

Concerning a possible deviation from random mating, the observed distribution of the three mating types given by Gm(a) alone, is given in

Table 8 Distribution of Gm(a) types in earlier and present family material

Mating type	Authors	Family	Exp. no. of families	Obs. no. of families	χ^2	D.F.	P
Gm(a) × Gm(a)	*Mäkelä and Tiilikainen* (1959)	All children Gm(a)	27.675	27	0.050	1	0.99>P>0.98
		Some children Gm($\overline{a}$)	14.325	15			
	Linnet-Jepsen, Galatius-Jensen and Hauge (1958)	All children Gm(a)	38.148	40	0.307	1	0.70>P>0.50
		Some children Gm($\overline{a}$)	16.852	15			
	Present paper	All children Gm(a)	16.529	18	0.386	1	0.70>P>0.50
		Some children Gm($\overline{a}$)	8.471	7			
Gm(a) × Gm($\overline{a}$)	*Mäkelä and Tiilikainen* (1959)	All children Gm(a)	14.202	17	1.034	1	0.50>P>0.30
		Some children Gm($\overline{a}$)	18.798	16			
	Linnet-Jepsen, Galatius-Jensen and Hauge (1958)	All children Gm(a)	36.325	40	0.642	1	0.50>P>0.30
		Some children Gm($\overline{a}$)	55.675	52			
	Present paper	All children Gm(a)	9.988	15	3.992	1	0.05>P>0.02
		Some children Gm($\overline{a}$)	17.012	12			
Gm($\overline{a}$) × Gm($\overline{a}$)	*Mäkelä and Tiilikainen* (1959)	Some children Gm(a)	0.0	0			
		All children Gm($\overline{a}$)	9.0	9			
	Linnet-Jepsen, Galatius-Jensen and Hauge (1958)	Some children Gm(a)	0.0	0			
		All children Gm($\overline{a}$)	34.0	34			
	Present paper	Some children Gm(a)	0.0	0			
		All children Gm($\overline{a}$)	8.0	8			
				325	6.411	6	0.50>P>0.30

Table 9

Distribution of children in 181 families containing at least one Gm($\overline{a}$) child, selected from a total of 353 families (table 8)

Matings	Authors	Gm(a) Exp.	Gm(a) Obs.	Gm($\overline{a}$) Exp.	Gm($\overline{a}$) Obs.	χ^2	D.F.	P
Gm(a) × Gm(a)	*Mäkelä and Tiilikainen* (1959)	33.131	34	20.869	20	0.055	1	0.90>P>0.80
	Linnet-Jepsen, Galatius-Jensen and Hauge (1958)	20.411	18	18.589	21	0.598	1	0.50>P>0.30
	Present paper	12.7	15	9.300	7	0.986	1	0.50>P>0.30
Gm(a) × Gm($\overline{a}$)	*Mäkelä and Tiilikainen* (1959)	18.851	20	27.149	26	0.119	1	0.70>P>0.50
	Linnet-Jepsen, Galatius-Jensen and Hauge (1958)	50.281	48	79.719	82	0.168	1	0.70>P>0.50
	Present paper	13.397	13	19.603	20	0.020	1	0.90>P>0.80
Gm($\overline{a}$) × Gm($\overline{a}$)	*Mäkelä and Tiilikainen* (1959)	0.0	0	26.0	26			
	Linnet-Jepsen, Galatius-Jensen and Hauge (1958)	0.0	0	93.0	93			
	Present paper	0.0	0	27.0	27			
			148		322	1.945	6	P > 0.90

table 8 for 325 Scandinavian and Finnish families. The numbers of Gm(a) × Gm(a), Gm(a) × Gm($\bar{a}$), and Gm($\bar{a}$) × Gm($\bar{a}$) matings are 122 (115.12), 152 (156.02), and 51 (53.86), respectively. The expected numbers, which are shown in brackets, were calculated by considering separately the Scandinavian and Finnish families, and applying the Gm(a) frequencies found in these two regions. (As indicated below, the Gm(a) frequency seems to be substantially higher in Finland than in Denmark, Norway and Sweden.)

When considering the phenotypes defined by all three antisera, anti-Gm(a), anti-Gm(x), and anti-Gm(b), only 52 matings are known to us. In table 2 these are arranged in such a way as to bring out any possible deviation from random mating. The expected numbers, as calculated from the observed distribution of phenotypes among the parents, are shown in brackets. The agreement with expectation appears good.

Value of the Gm-system in human genetics. The "usefulness" of the Gm-system in problems of identity may be measured by the sum of the squares of the possible phenotype frequencies (*Fisher*, 1951). By comparison of the eight phenotypes given by the three antisera anti-Gm(a), anti-Gm(x), and anti-Gm(b), the value 0.333 or 33.3% is obtained. This number gives the proportion of cases in which discrimination between two random individuals fails.

The corresponding number in the case of diagnosis of zygosity of twins, is 58.34%. By interchange of children it is 60.74%. In cases of disputed paternity it is 72.72%.

Population frequencies

It has been shown earlier (*Grubb*, 1956) that the frequency of Gm(a) individuals in Eskimos is higher than in Europeans. Among 74 individuals *Grubb* found 70 (or 94.6%) to be Gm(a). To assess whether any heterogeneity is apparent within the available European material, the results of *Moullec et al.* (1956), *Podliachouk et al.* (1958), on a total of 600 French individuals, those of *Mäkelä and Tiilikainen* (1959) on 477 Finns, and those on Danes (*Linnet-Jepsen et al.*, 1958), Norwegians (*Harboe and Lundevall*, 1959, present material), and Swedes (*Grubb and Laurell*, 1956) comprising a total of 1963 individuals, were compared. The frequencies of Gm(a) individuals in these three groups (French, Finns and Scandinavians) are 0.5583, 0.6499, and 0.5772, and thus differ considerably. The Finnish individuals show a somewhat higher frequency of Gm(a) than the other two groups. Comparisons Scandinavia-France, Scandinavia-Finland, Fin-

land-France, gave χ^2 (1) = 0.666 (0.50 > P > 0.30); χ^2 (1) = 8.404 (P < 0.01); and χ^2 (1) = 11.748 (P < 0.001), respectively.

The Scandinavian material of 1963 unrelated individuals includes 1084 Danes, 519 Norwegians and 360 Swedes. A test for heterogeneity between the three Scandinavian countries did not reveal any significant difference.

Summary

Three factors a, b, and x of the Gm system are considered in 52 Norwegian families with 149 children, and in 199 unrelated individuals. This data and some material of earlier writers is discussed with regard to current views on the genetics of the Gm types, the "usefulness" of the system, and population frequencies.

Zusammenfassung

Drei Faktoren des Gm-Systems werden bei 52 norwegischen Familien mit 149 Kindern sowie 199 nicht miteinander verwandten Personen betrachtet. Diese Daten werden zusammen mit dem Material früherer Untersuchungen nach folgenden Gesichtspunkten diskutiert: 1. Allgemeine Ansichten über die Erblichkeit der Gm-Typen, 2. «Nützlichkeit» des Systems, 3. Häufigkeit in der Bevölkerung.

Résumé

Les trois facteurs du système Gm ont été examinés dans 52 familles norvégiennes comprenant 149 enfants et 199 individus non apparentés. Les résultats des constatations d'autres auteurs sont discutés en tenant compte des opinions actuelles sur la génétique des types Gm, l'utilité de ce système et leurs fréquences dans la population.

REFERENCES

Fisher, R. A.: Standard calculations for evaluating a blood group system. Heredity *5:* 95–102 (1951).

Fudenberg, H.: (Personal comm.) (1960).

Grubb, R. and Laurell, A. B.: Hereditary serological human serum groups. Acta path. microbiol.. scand. *39:* 390–398 (1956).

Hald, A.: Statistical theory with engineering applications. S. 698. (J. Wiley & Sons Inc. New York. 1952).

Harboe, M.: a) A new haemagglutinating substance in the Gm system, anti-Gm. Nature, Lond. *183:* 1468–1469 (1959). – b) A new haemagglutinating substance in the Gm system, anti-Gm^b. Acta path. microbiol. scand. *47:* 191–198 (1959).

Harboe, M. and Lundevall, J.: A new type in the Gm system. Acta path. microbiol. scand. *45:* 357–370 (1959).

Henningsen, K.: personal communication.

Linnet-Jepsen, P.; Galatius-Jensen, F. and Hauge, M.: On the inheritance of the Gm serum group. Acta genet. *8:* 164–196 (1958).

Moullec, J.; Kherumian, R.; Sutton, E. et Espagnon, P.: Contribution à l'étude du facteur de groupe Gm^a du plasma humaine. Rev. Hémat. *11:* 512–517 (1956).

Mäkelä, O. and Tiilikainen, A.: Inheritance of the Gm serum group. Ann. Med. exp. Fenn. *37:* 180 (1959).

Podliachouk, L.; Jaqueline, F. et Eyquem, A.: Le facteur sérique Gm^a au cours des rhumatismes inflammatoires chroniques. Ann. Inst. Pasteur *94:* 590–597 (1958).

Race, R.R. and Sanger, R.: Blood groups in man. p. 377 (Blackwell, Oxford 1958).

Steinberg, A.G.; Giles, B.D. and Stauffer, R.: A Gm-like factor present in Negroes and rare or absent in Whites: Its relation to Gm^a and Gm^x. Amer. J. hum. Genet. *12:* 44–51 (1960).

ACKNOWLEDGEMENTS

Thanks are due to Drs. *H. Fudenberg, M. Harboe, O. Hartmann, J. Lundevall, A.G. Steinberg,* for generous gifts of typing serum, and to the individuals and families who by contributing blood samples made the study possible.

Authors' address: Dr. B. Brandtzæg and Dr. J. Mohr, University Institute of Human Genetics, *Oslo* (Norway).

Acta genet. *11:* 126–132 (1961)

From the Institute for Medical Genetics and the Department of Serology and Bacteriology, University of Helsinki, Finland

SERUM PROTEIN VARIATIONS IN MONKEYS

By LARS BECKMAN, GÖSTA HOLMGREN, O. MÄKELÄ and R. LEHTOVAARA

1. Introduction

After *Smithies*' discovery of the human haptoglobin groups by means of starch gel electrophoresis (*Smithies*, 1955, a and b) and the finding that they were genetically controlled (*Smithies and Walker*, 1955), several other serum protein polymorphisms have been described in humans. *Smithies* (1957) found variations in the β-globulin region. *Smithies and Hiller* (1959) and *Giblett, Hickman and Smithies* (1958) have shown that the variable β-globulins are ironbinding proteins (transferrins or siderophilins). Family data showing the genetic control of human transferrin have been presented by *Smithies and Hiller* (1959). An unusual serum protein migrating slightly faster than the fast α_2 component has been described by *Frazer, Harris and Robson* (1959). *Morell and Scheinberg* (1960) found four different ceruloplasmin components in human sera. They suggested that the ceruloplasmin variations are genetic in origin.

The haptoglobin types of apes and monkeys have been studied by *Blumberg* (1960), *Arends and Rodriguez* (1960) and *Mäkelä, Renkonen and Salonen* (1960). All animals (altogether more than 250) were found to have the haptoglobin phenotype Hp 1–1. *Beckman and Cedermark* (1960), studying 30 Macaca irus, have found a haptoglobin polymorphism in this species. Some individuals had a pattern similar to the human Hp 2–1 mod. phenotype. Of the animals studied previously, only one belonged to the species Macaca irus.

Blumberg (1960) has studied the transferrins of Macaca mulatta (syn. Macaca rhesus). He found several different transferrin patterns. There is one common type with one band only and another type with a fast moving band

in addition to the common single transferrin. *Beckman, Hirschfeld and Söderberg* (1960) have examined the transferrins of 36 Macaca irus. Five different transferrin components and eight different phenotypes were found. In addition to the normally occurring single transferrin, three different fast components could be distinguished. *Lai and Kirk* (1960) have studied the transferrin variations of Macaca mulatta and Macaca irus. They observed several different types in both species and a higher frequency of fast components in Macaca irus.

Blumberg (1960) has also studied prealbumin polymorphism in monkeys. Three different types were observed.

2. This investigation

In this study the serum protein variations in 14 Macaca rhesus, 10 Macaca radiata and 10 Macaca irus have been examined by means of starch gel electrophoresis and *Poulik's* (1957) buffer system. The haptoglobins of the Macaca rhesus and Macaca radiata samples were previously studied by *Mäkelä, Renkonen and Salonen* (1960).

A renewed test for the haptoglobins of these animals revealed haptoglobin patterns other than the typical Hp 1–1 pattern in two Macaca radiata and one Macaca rhesus. In the Macaca irus sample seven individuals showed more than the ordinary Hp 1–1 band. The different haptoglobin patterns have been summarized in fig. 1. Strip 1 in the figure shows the common Hp 1–1 pattern. Strip 2 shows the type in Macaca irus previously described by *Beckman and Cedermark* (1960). The faster of the two extra bands is stronger than the corresponding band in the pattern of strip 3, which was found in one of the ten newly examined Macaca irus. Strip 4 shows a pattern that has been observed in six Macaca irus of the present series. No band corresponding to the faster of the additional bands of strips 2 and 3 could be detected. Strips 5 and 6 show patterns found in one Macaca rhesus and one Macaca radiata. The slowest band of strip 5 is more strongly developed. It appears that the faster of the two additional bands in strips 5 and 6 migrates slightly faster than those of types 2 and 3. Strip 7 (Macaca radiata) shows a single slow band in addition to the Hp 1–1 band. A single band different from that of strip 7 was also found in the serum from a chimpanzee (strip 8). Finally on strip 9 the human Hp 2–1 pattern is shown. Previously *Beckman and Cedermark* (1960) assumed that the bands of type 2 corresponded to the Hp 2–1 bands. Repeated double-runs in this study have led us to the conclusion that there are slight differences between the slow components of

human Hp 2–1 and Macacus haptoglobin patterns, while the Hp 1–1 band occupies the same position.

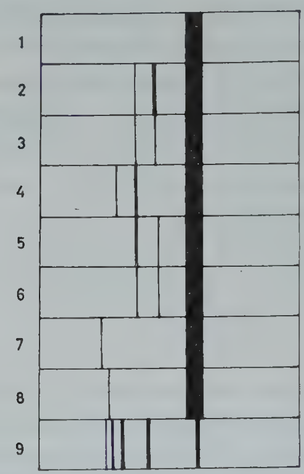


Fig. 1

Diagrammatic representation of benzidine staining patterns. Strip 1 shows the Hp 1–1 pattern; strips 2–4, Macaca irus; strip 5, Macaca rhesus; strips 6–7, Macaca radiata; strip 8, Chimpanzee and strip 9 the human Hp 2–1 pattern

In both Macaca rhesus and Macaca radiata transferrin variations were observed. In Macaca rhesus three distinct types could be distinguished (fig. 2). Only one individual had type 3, while four individuals were of type 2 and eight individuals of type 1. The transferrin pattern of one serum sample could not be safely established, due to strong haemolysis.

In Macaca radiata three different types were found (cf. fig. 2), four individuals with a slow band, two with a fast band and finally four individuals possessing both transferrin components. The type with two bands may be a transferrin heterozygote and the two other types the corresponding homozygotes.

In the ten Macaca irus three different transferrin types were found, two of which (2 and 3) have been observed earlier by *Beckman, Hirschfeld and Söderberg* (1960). The faster component, which is rather frequent in this sample was previously found in only one out of 36 individuals. As also the haptoglobin types of this Macaca irus sample are different from those of the previous series, it seems reasonable to assume that we are not dealing with random samples, but, rather small groups of related individuals.

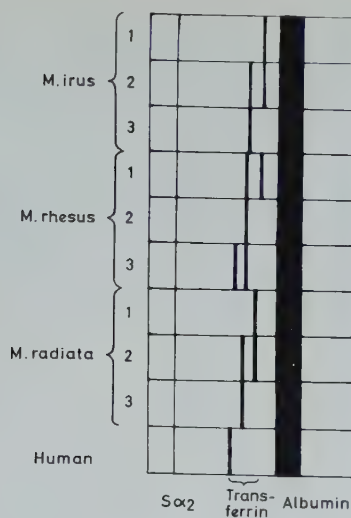


Fig. 2

Diagrammatic representation of transferrin patterns.

When the transferrin patterns of the three Macacus species were compared, rather interesting results emerged. Heterozygous types from the three monkey species were examined on the same gel together with a human serum. A photo of the resulting gel is found in fig. 3. The transferrin patterns of the three Macacus species are rather similar. It should be noted, however, that there are slight differences in the electrophoretic mobility of all the

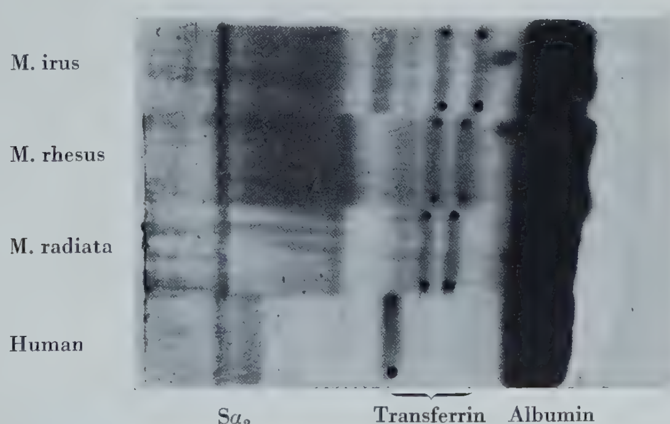


Fig. 3

Photograph of a starch gel stained with amidoblack, showing sera from three different Macacus species run together with a human serum of type Tf C.

components observed. Human transferrin migrates slower than that of monkeys. In agreement with the results of *Lai and Kirk* (1960) we have found that Macaca irus more frequently has fast moving transferrin components compared to Macaca rhesus.

The ceruloplasmin was stained with paraphenylenediamine. In human as well as in monkey sera we have only found one ceruloplasmin component. This component has the same electrophoretic mobility in humans and monkeys and thus may serve as a good reference protein for measurements of the mobility of transferrins. The ceruloplasmin moves somewhat faster than the human transferrin C and slower than most monkey transferrins.

3. *Discussion*

In this study several different haptoglobin patterns have been observed in monkeys. The patterns are quite reproducible from a technical point of view. Apart from the type described by *Beckman and Cedermark* (1960) no other workers have reported haptoglobin variations in apes or monkeys. We consider it rather unlikely that all the different patterns can be artificial in origin although this possibility cannot at present be ruled out. Repeated double runs using different haemoglobin solutions from humans and monkeys gave the same result. Double runs together with the concentrated haemolysate of red cells revealed that the faint benzidine staining bands did not originate from the haemolysate. The same results were found independently in two different laboratories (Uppsala and Helsinki). Also in man many different haptoglobin patterns have been reported from various populations (cf. *Blumberg, Allison and Garry*, 1959) suggesting that there may exist several different mutations besides the commonly occurring Hp 1- and Hp 2-genes. We would like to point out that many of the haptoglobin components in monkeys stain very weakly even with benzidine and that they are developed later than the very strong Hp 1–1 band. We have found it easiest to observe the faint bands if the gel is placed on a glass plate with a sheet of white paper below and with strong light on the gel surface. In this way we have also been able to detect very weak haptoglobin bands (type Hp 2–2) in a human serum previously classified as Hp-O.

The electrophoretic mobility of the transferrins in the three monkey species is rather similar. The transferrins in humans and chimpanzees (*Boyer and Young*, 1960) are similar and migrate considerably slower than the monkey transferrins. *Boyer and Young* (1960) have also found that some components in humans and chimpanzees are apparantly identical. Thus the existing observations of transferrins in primates indicate that the trans-

ferrins may be genetic markers especially well suited for phylogenetical studies. In this connection it must be emphasized that with unidimensional electrophoresis it is not always possible to get unambiguous results concerning the identity of electrophoretic behaviour of two serum proteins. With repeated double runs for different periods of time, however, the identity of different components can be established with a rather high degree of probability. As mentioned above, no definite evidence for identity of the transferrin components of the three Macacus species has emerged. Nor has it been possible with certainty to demonstrate any transferrin components occurring in both monkeys and humans. The finding by *Boyer and Young* (1960) shows, however, that there may exist a series of overlapping patterns of transferrin polymorphism in different primate groups. Possibly, there might also be a phylogenetical trend, so that the higher primates have slow moving transferrins and lower primates such as Macacus monkeys and baboons (*Blumberg*, 1960), have faster migrating transferrins.

It is notable that the patterns of iron-binding proteins in primates may vary in electrophoretic mobility from that of the haptoglobin (in chimpanzees) to very fast components close to the postalbumins (in monkeys), while the copperbinding protein, ceruloplasmin, shows no variation.

Summary

The serum protein patterns of three different species of Macacus monkeys have been studied by means of starch gel electrophoresis. Several different benzidine staining patterns were observed in different species. No identity between the transferrin components of the three species was found. The ceruloplasmin of all primates studied shows no variations. It is concluded that there may be a phylogenetical trend so that lower primate groups have faster moving transferrins than higher primates.

Zusammenfassung

Mit Hilfe der Stärkegel-Elektrophorese wurden die Serum-Proteingruppen dreier verschiedener Arten von Macacus-Affen untersucht, und es wurden bei Benzidin-Färbung mehrere verschiedene Muster beachtet. Die Transferrin-Komponenten der drei Arten zeigten keine Identität. Dagegen wies das Coeruloplasmin aller untersuchten Primaten keine Unterschiede auf. Möglicherweise besteht ein phylogenetischer Trend dergestalt, daß niedrige Primaten-Gruppen rascher wandernde Transferrine haben als höhere Primaten.

Résumé

Le comportement des protéines sériques a été examiné chez trois différentes espèces de singes Macacus à l'aide de l'électrophorèse avec gel amidon. Plusieurs types colorant la benzidine ont été trouvés dans plusieurs espèces. Il n'y a pas d'identité entre les composantes de la transferrine chez les trois espèces. La ceruloplasmine ne montre pas de variation chez les primates. Il est probable que du point de vue phylogénétique, les primates inférieurs ont des transferrines se déplaçant plus rapidement que celles des primates supérieurs.

REFERENCES

Arends, T. and Rodriguez, M.L.G. de: Haptoglobin in Monkeys. Nature, London *185:* 325 (1960).

Beckman, L. and Cedermark, G.: Haptoglobin types in Macaca irus. Acta genet. *10:* 23 (1960).

Beckman, L.; Hirschfeld, J. and Söderberg, U.: Transferrin variations in sera of Macaca irus. Acta path. microbiol. scand. (in press).

Blumberg, B.S.; Allison, A.C. and Garry, B.: The haptoglobins and haemoglobins of Alaskan Eskimos and Indians. Ann. hum. genet. *23:* 349 (1959).

Blumberg, B.S.: Biochemical polymorphisms in animals: haptoglobins and transferrins. Proc. Soc. exp. Biol., N.Y. *104:* 25 (1960).

Boyer, S.H. and Young, W.J.: β-globulin polymorphism in Chimpanzees. Nature, London *187:* 1035 (1960).

Frazer, G.R.; Harris, H. and Robson, E.B.: A new genetically determined plasma-protein in man. Lancet *i:* 1012 (1959).

Giblett, E.R.; Hickman, C.G. and Smithies, O.: Serum transferrins. Nature, London *183:* 1589 (1959).

Lai, L.Y.C. and Kirk, R.L.: β-globulins variants in two species of Monkeys. Nature, London *188:* 673 (1960).

Morell, A.G. and Scheinberg, I.H.: Heterogeneity of human ceruloplasmin. Science *131:* 930 (1960).

Mäkelä, O.; Renkonen, O.-V. and Salonen, E.: Electrophoretic patterns of haptoglobins in apes. Nature, London *185:* 852 (1960).

Poulik, M.D.: Starch gel electrophoresis in a discontinous system of buffers. Nature, London *180:* 1477 (1957).

Smithies, O.: a) Grouped variations in the occurrence of new protein components in normal human serum. Nature, London *175:* 307 (1955). – b) Zone electrophoresis in starch gels; group variations in the serum proteins of normal human adults. Biochem. J. *61:* 629 (1955).

Smithies, O. and Walker, N.F.: Genetic control of some serum proteins in normal humans. Nature, London *176:* 1265 (1955).

Smithies, O.: Variations in human serum-globulins. Nature, London *180:* 1482 (1957).

Smithies, O. and Hiller, O.: The genetic control of transferrins in humans. Biochem. J. *72:* 121 (1959).

Authors' addresses: Dr. L. Beckman and Dr. G. Holmgren, Institutionen för Medicinsk Genetik, 24 V. Ågatan, *Uppsala;* Dr. O. Mäkelä and Dr. R. Lehtovaara, Institutum Sero-Bacteriologicum Universitatis, *Helsinki* (Finland).

Acta genet. *11:* 133—136 (1961)

From the Institute for Medical Genetics, Uppsala

OSTEOGENESIS IMPERFECTA AND BLOOD GROUPS

By G. SMÅRS, L. BECKMAN and J. A. BÖÖK

Introduction

In 1788 *O. J. Ekman* described a Swedish family in which seven members in four generations showed severe bone fragility. *Ekman*'s treatise, in which the affection was termed congenital osteomalacia, is reviewed in the work by *Seedorff* (1949). *Axmann* (1831) gave a clear description of bone fragility combined with blue sclerae and hyperlaxibility with a tendency to articular dislocations and slender body constitution.

In 1833 *Lobstein* of Strassburg described hereditary bone fragility, which he named osteopsathyrosis idiopathica and the affection has been called *Lobstein*'s disease after him. In 1849 *Vrolik* reported a case of severe congenital bone fragility in a child who died three days after birth. The severe congenital form was named osteogenesis imperfecta after his description or *Vrolik*'s disease.

In 1900 *Looser* drew the conclusion, based upon similarities between the histological findings, that the two types of bone fragility were identical. He suggested that the name osteogenesis imperfecta, which earlier had been reserved for the severe form described by *Vrolik*, should also be used for the more moderate form of brittle bones (called by *Lobstein* osteopsathyrosis idiopathica). For practical reasons *Looser* considered that it might still be appropriate to differentiate between the two extreme forms of the disease: Osteogenesis imperfecta congenita and osteogenesis imperfecta tarda. This nomenclature has been generally accepted.

All the manifestations of the syndrome are thought to originate from defects in the primary elements of the mesenchymal tissue.

Blue sclerotics in families with bone fragility were first reported by *Axmann* (1831) and later by *Spurway* (1896) and *Eddowes* (1900). An increased frequency of deafness in individuals with osteogenesis imperfecta was found by *Adair-Dighton* (1912), *Bronson* (1917) and *van der Hoeve* and *de Kleyn* (1918). *Seedorff* (1949) studied the inheritance of osteogenesis imperfecta in a large number of Danish families.

The disease is inherited as a dominant trait with nearly complete penetrance. The expressivity of the different symptoms of the syndrome is very variable (cf. *Smårs* 1960).

Mohr (1954) has studied the linkage relations of osteogenesis imperfecta with sex, seven blood group systems and taste sensitivity to phenylthiourea. He found no significant indication of linkage.

This investigation

The present work is a part of a study of osteogenesis imperfecta in Sweden.

Families with cases of osteogenesis imperfecta were collected from all over Sweden by one of us *(Smårs)*. The material has a high degree of completeness (cf. *Smårs* 1960).

The blood group tests have been performed at the Blood Group Serological Department, State Laboratory for Forensic Chemistry, Stockholm.

The relation between osteogenesis imperfecta and blood groups is shown in table 1. No significant associations were found.

Table 1

Osteogenesis imperfecta in relation to blood groups
(+) = osteogenesis imperfecta, (—) = unaffected

	R_1r	R_2r	rr	R_1R_1	R_1R_2	R_2R_2	R_0r	R′r	R″r
(+)	48	19	18	35	21	3	5	1	2
(—)	70	28	36	40	32	6	6	3	4
	118	47	54	75	53	9	11	4	6

	A_1	A_2	B	A_1B	A_2B	O
(+)	50	12	21	5	1	63
(—)	88	24	18	6	1	88
	138	36	39	11	2	151

	M	MN	N	P+	P—	K+	K—
(+)	48	80	24	117	35	11	141
(—)	77	108	40	167	58	15	210
	125	188	64	284	93	26	351

The linkage relations between osteogenesis imperfecta and blood group markers were studied by means of the sib pair method. In agreement with the previous findings by *Mohr* we found no indications of linkage. The primary material is filed at the Institute for Medical Genetics, Uppsala, Sweden.

The blood group markers were found to be valuable for the solution of the important, though rarely occurring, problem of families with apparently healthy parents but with many affected children. Data for such a family are given in fig. 1. Both parents were classified as normal. The mother had one single fracture when falling from a bicycle. She also had slightly impaired hearing in one ear. Four of the six children had osteogenesis imperfecta. In two of the cases the sclerae were blue. Two of the children were also rather handicapped by the disease.

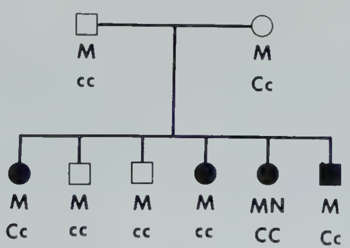


Fig. 1

Pedigree of a family with apparently unaffected parents and four affected children. The fifth child is illegitimate; the paternity of the husband is excluded according to the MN-system and the C-factor of the Rhesus-system. Black symbols indicate osteogenesis imperfecta.

As there are four affected children in the family, mutation can be ruled out as a source of explanation. Based upon the blood group findings, one of the affected children was shown to be genetically incompatible with the father according to the MN- and Rhesus-systems. Obviously the father can not have transmitted the osteogenesis imperfecta gene to this child. Because of the extreme rarity of the gene it is highly unlikely that the unknown father also had this gene. Thus the illegitimate child should have inherited it from its mother and the conclusion would be that we are dealing with a family where one of the parents (the mother) possesses the gene for osteogenesis imperfecta, but that the expression of the trait is modified, presumably by some other gene. There is, however, no need to consider the hypothesis of a special recessive variant of the disease in the above mentioned family.

Summary

The relations between blood groups and osteogenesis imperfecta were studied in Swedish families comprising 377 individuals. No significant associations and linkage relations were found. Blood group markers have proved to be valuable when elucidating modifications in the expressivity of osteogenesis imperfecta.

Zusammenfassung

Die Zusammenhänge zwischen Blutgruppen und Osteogenesis imperfecta wurden bei schwedischen Familien untersucht. Das Untersuchungsmaterial umfaßte 377 Personen. Signifikante Korrelationen und Koppelungsbeziehungen wurden nicht gefunden. Blutgruppen-Markierer erwiesen sich als wertvoll, um Modifikationen im Auftreten der Osteogenesis imperfecta zu erkennen.

Résumé

Les relations entre groupes sanguins et osteogenesis imperfecta ont été étudiées dans des familles suédoises comprenant 377 individus en tout. Aucune association ou linkage n'ont pu être mis en évidence. Des groupes sanguins servant de marqueurs ont montré une certaine importance lorsqu'il s'agissait de se rendre compte des modifications de l'osteogenesis imperfecta du point de vue expression.

REFERENCES

1. *Adair-Dighton, C. A.:* Four generations of blue sclerotics. Ophtalmoscope *10:* 188–189 (1912).
2. *Axmann, E.:* Merkwürdige Fragilität der Knochen ohne dyskrasische Ursache als krankhafte Eigentümlichkeit dreier Geschwister. Ann. J. ges. Heilk. Jahrg. *4:* 58 (1831).
3. *Bronson, E.:* On fragilitas ossium and its association with blue sclerotics and otosclerosis. Edinb. med. J. *18:* 240–281 (1917).
4. *Eddowes, A.:* Dark sclerotics and fragilitas ossium. Brit. med. J. *2:* 222 (1900).
5. *Ekman, O. J.:* Descriptionem et casus aliquot osteomalacia sistens. Med. Diss. (Uppsaliae 1788).
6. *Hoeve van der, J. und Kleyn de:* Blaue Sclerae, Knochenbrüchigkeit und Schwerhörigkeit. Arch. Ophtal., Paris *95:* 81–93 (1918).
7. *Lobstein, J.G.:* Lehrbuch der pathologischen Anatomie. (Stuttgart 1835).
8. *Looser, E.:* Zur Kenntnis der Osteogenesis imperfecta et tarda. Mitt. Grenzgeb. Med. Chir. *15:* 161 (1906).
9. *Mohr, J.:* A study of linkage in man. (Munksgaard, København 1953.)
10. *Seedorff, H. S.:* Osteogenesis imperfecta. (Universitetsforlaget i Århus, 1949.)
11. *Smårs, G.:* Osteogenesis imperfecta (in press).
12. *Spurway, J.:* Hereditary tendency to fracture. Brit. med. J. *2:* 844 (1896).

Authors' address: Dr. G. Smårs, Dr. L. Beckman and Prof. J. A. Böök, Institutionen för Medicinsk Genetik, V. Ågatan 24, *Uppsala* (Sweden).

Acta genet. *11:* 137–153 (1961)

From the University Hospital, Medical Dept. (Head: Prof. Dr. L. A. Hulst)
and the Institute of Physical Anthropology and Human Genetics
(Head: Dr. J. Huizinga); State University, Utrecht-Holland

FAMILIAL OCCURRENCE OF PHAEOCHROMOCYTOMA

By M. SMITS and J. HUIZINGA

A. Introduction

During the last few years, the clinical picture of phaeochromocytoma has evoked increasing interest among clinicians. Important progress has been made in the diagnostic field which enables us to approximate the diagnosis closely and, in most of the cases, to make it practically certain that we are dealing with a form of hypertension curable by operation (with a good prognosis!) which, thanks to several new drugs, has no significant risk.

The familial occurrence of phaeochromocytoma has been known for a rather considerable time. In 1947 *Calkins and Howard* (1) reported the first case. Since then, as far as we know now, eight other reports have been published concerning more than one case of phaeochromocytoma in one family (2, 3, 4, 5, 6, 7, 8). Yet we believe that the familial occurrence of the underlying disease has not obtained its due attention. This is made clear by the fact that in many publications concerning cases of phaeochromocytoma data about the family history are totally omitted (for example, 8).

As we had, in 1957, the opportunity to observe a patient who had bilateral adrenal phaeochromocytoma and whose family history was very impressive, we are able, thanks to the co-operative attitude of this family in undergoing an extensive examination, to present here this case of familial occurrence of phaeochromocytoma.

This communication concerns a rather large family in which we found phaeochromocytoma in four persons (all diagnoses could be verified by pathologic-anatomical investigation); moreover, we could collect strong evidence that this disease has most likely existed in ten other members of the family during their lives (these ten individuals were already deceased when we started our investigations. The data on which we base this state-

ment consisted of information given to us by members of the family independently of each other, inmates, family doctors, specialists and nurses who have known and/or treated the patients concerned. We also tried to gather all the data to be found in hospital archives on all those persons who had ever been hospitalized before.

This article will deal only with the familial occurrence of phaeochromocytoma. A description of historical, embryological, pathologic-anatomical and pharmacologic particularities of the disease will not be given. The clinical picture, the diagnostic problems, the complicating diseases and the therapy will not be discussed either.

Figure 1 gives a survey of the family investigated. The individuals indicated with † were all deceased at the start of our investigations. When one generation (the generations are indicated I, II, etc.) comprises more than one group of sibs, these groups are indicated with a type mark (M, N, P, etc.). The children in every household are numbered (1, 2, 3, etc.), the youngest last; in generation V, however, all children are numbered (1–18) in succession.

B. Working method

All children over ten years of age and all adults, direct offspring of the "founder" of the family, I_1, underwent an extensive examination: anamnesis, general somatic examination extended with haemogram, determination of blood group, cholesterol, glucose tolerance test, erythrocyte sedimentation rate, X-ray of thorax, including size and configuration of the heart, electrocardiogram, routine urine tests and examination of the ocular fundi.

The blood pressure was measured in the lying, sitting and standing position, respectively. If there were reasons for doing so, we extended this scheme further (e.g., intravenous pyelography, basal metabolic rate, etc.). In nearly all persons we also did a histamine test (where desirable, a regitine test) and determined, twice in every person, the catecholamines in 24 hours' urine, following *Burn*'s method (9) (slightly modified, as done in the laboratories of the Utrecht National Institute of Health). The latter determinations were made on two consecutive days; on the second day, however, a histamine test was made and, moreover, the urine formed during the two hours after histamine administration was examined separately.

For those allied by marriage, among whose children there were certainly or probably phaeochromocytoma affected persons, the same scheme was followed. The other members allied by marriage were examined less ex-

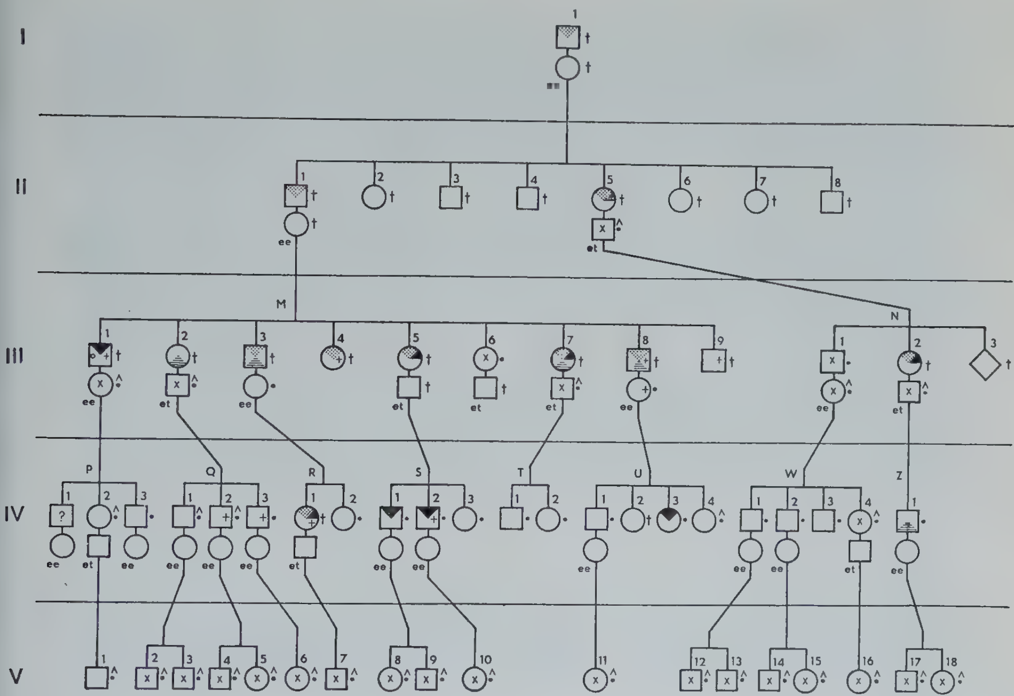


Fig. 1. Familial occurrence of phaeochromocytoma in a Dutch family.

Explanation of symbols

	male		female		sex unknown
	verified phaeochromocytoma		probable phaeochromocytoma		eclampsia-like picture
	diabetes mellitus	+	enlarged thyroid gland	O	carcinoma of thyroid gland
•	personally examined	×	no histamine test	Λ	catecholamines not determined
†	deceased	ee	wife	et	husband
?	not examined				

tensively (anamnesis, general somatic examination); those of generation IV were only interviewed anamnestically.

In infants and younger children, for psychological reasons, injections, punctures and admittance to the hospital were avoided and the investigations limited to a hetero-anamnesis (parents) and general somatic examination.

In the relatives by marriage of generation IV and in all members of generation V there were no suspective symptoms at all for phaeochromocytoma. The whole family, however, will have our constant attention in the future.

In all the individuals examined, we looked for "stigmata degenerationis", signs of morbus *Recklinghausen*, morbus *Hippel-Lindau*, etc.

The persons are indicated as follows: e.g., IV S_1 means generation IV, group of siblings S, number 1; this man was the "probandus" of the family-tree.

Two persons (III M_6 and III N_1) refused intravenous injection of histamine and/or regitine.

In this pedigree any form of consanguinity could be excluded, thanks to the help of the Public Record Office in The Hague (the whole family-tree was reconstructed) and by extensively interrogating all members of the family.

C. Description of the family

The description of the family starts with that of the probandus, IV S_1, followed by a brief description of the whole family descended from I_1. For the sake of brevity those individuals who did not, after extensive examination, show any reason for suspicion, are not mentioned.

The description is started with the literally cited communications about the symptoms of the disease, just as we obtained them from Mr III $M_{7\ et}$. This man has lived in the family circle for many years and has accurately observed all signs and particularities of the disease (also on his own wife). As the attacks of illness in all affected individuals were always accompanied by heavy trembling (apart from the attacks, signs of trembling were never seen in the family), they used to call the disease "the trembles"[1]). An attack of "the trembles" was a well known and frequently occurring phenomenon.

Mr III $M_{7\ et}$:

"Suddenly the person concerned grew pale, really dead-pale and started to tremble in a clearly visible way. When this occurred during lunch or dinner, one could see the fork

[1]) This is in our opinion the best equivalent in English for the Dutch word "de beef" used by the patients and their relatives.

shaking in the patient's hand. He then complained of heavy heart-beating and headaches. Many of the affected persons felt inclined to vomit. After that, the patient started perspiring while the attack subsided. This sweating was very heavy. It was always so heavy that one could distinctly smell the odour of sweat. Everyone was more or less familiar with these phenomena. One used to say, "Oh, he has the trembles again; it will soon be over". Many times it struck me that the attacks came when the patient ate a bit too much; on the other hand, I have often seen the attacks come when the patient had an empty stomach. The attacks sometimes took a couple of minutes, sometimes half an hour. Often there were several attacks on one and the same day. After such an attack the patients looked dead-beat and worn out, and they felt miserable for a couple of hours. I have noticed that all my relatives who had "the trembles" later on got diabetes, especially when the attacks grew more and more frequent and serious, and this was gradually the course in all cases.

I have seen in almost every case the following development: after having had "the trembles" for 8–10 years, they got diabetes; 5–6 years later, they died."

It was impressive to hear this man telling his tale of what he had seen for many years: identical symptoms in his own wife, his father-in-law, three brothers-in-law, two sisters-in-law and, later, in two nephews and in a niece.

IV S_1, male, 31 years old.

Typical pattern of complaints. All symptoms: attacks, rising blood pressure, histamine test, catecholamines, X-ray (presacral insufflation of air) were positive. Operation (Prof. Dr. *J.F. Nuboer*): at the left side two big tumours, at the right side one big tumour removed (two sessions). Pathologic-anatomical findings (Prof. Dr. *A. de Minjer*): phaeochromocytoma.

I_1, male, deceased 1899, 64 years of age.

As it appeared from verbal communications given by several relatives (his son, II_1, had often told it to III $M_{7\ et}$) this man surely suffered from attacks of "the trembles".

II_1, male, deceased 1931, 64 years of age.

Many relatives (his own children, sons- and daughters-in-law) remember having seen attacks of "the trembles" in II_1. Their description is clear and really typical. Also his sons III M_1, III M_3 and III M_8 often said: "We have the same disease as our father had".

II_5, female, deceased 1904, 31 years of age.

In the family she was known as having "the trembles". She died suddenly in the 8th month of her third pregnancy. The child was not born. Nothing is known about eventual eclampsia, high blood pressure or diabetes. Her husband (now 85 years old) told us that she had the same "trembles" as her father, I_1.

II_2, II_3, II_4, II_6, II_7, II_8 all died at young ages: six, three, six months, two, one and a half, and twelve years old respectively. This occurred during the years 1872–1892. No data are available.

III M_1, male, deceased 1952, 62 years of age.

Typical complaints and typical attacks were well known to the whole family. Post-mortem examinations: bilateral phaeochromocytoma and carcinoma of the thyroid gland.

III M_2, female, deceased 1954, 62 years of age.

She suffered as appeared from the archives of the hospital where she was observed in 1954 from diabetes mellitus and insufficiency of the coronary arteries. All her relatives confirm uniformly that definitely she did *not* have "the trembles".

III M_3, male, deceased 1954, 59 years of age.

According to the descriptions given by his wife, who is still alive, and by his daughter, IV R_2, and also by III $M_{7\ et}$, this man had typical attacks of "the trembles". He always tried to conceal that he was suffering from a disease. Afterwards he became diabetic and had a myocardial infarction.

III $M_{3\ ee}$, female, 61 years old.

She was extensively examined: no findings suspect for eventual hyperactivity of adrenal medulla.

III M_4, female, deceased 1926, 29 years of age.

According to comments given by many relations she was "worst of all; she was a poor wretch". In a medical statement given by a neurologist-psychiatrist (1921) we find: "extremely tired, emaciated, tremors, goitre, much vomiting, palpitations, very loud heart sounds". During the attacks she grew dead-pale ("like marble") and then perspired heavily, while she also had severe headache and vehement heart beats (communicated to us by III $M_{3\ ee}$ in whose house III M_4 stayed frequently). She died at home under the diagnosis: apoplexia cerebri with hemiparalysis. Blood pressure was never measured.

III M_5, female, deceased 1931, 30 years old.

Suffered seriously from "the trembles" and showed all the characteristic symptoms of the disease. She died suddenly 8–9 hours after her third delivery. No eclampsia-like symptoms. Diagnosis of family doctor: apoplexia.

III M_6, female, 56 years of age.

Never showed any symptoms of the disease. Is feeling quite well. After extensive examination no deviations were found. Catecholamines in (24 hours') urine: one time 325 μg, later 110 μg. Mrs. III M_6 refused to undergo an intravenous test (histamine, regitine). From these findings we cannot venture to draw any conclusions.

III M_7, female, deceased 1943, 37 years old.

Had typical attacks. The diagnosis "tumour of the adrenal medulla" had already been given as being likely by a family doctor in 1933, but he did not advise surgical treatment. (The first operation for phaeochromocytoma in the Netherlands took place in 1933 by Prof. Dr. *W.F. Suermondt*). The patient died, as II-para after a caesarean section due to eclamptic attacks, under the clinical picture of cerebral haemorrhagia. She had had diabetes since 1940.

III M_8, male, deceased 1950, 42 years old.

The whole family knew that he had attacks of "the trembles". The description of the symptoms is typical. From specialist statements we learned: he had a goitre and diabetes,

and paroxysmal atrial fibrillation. The doctors considered tumour of the adrenal. The patient died after operation of the right kidney because of renal tuberculosis. There was no adrenal tumour on the right side. A few hours after the intervention he suddenly grew bad and died. Obduction was refused by the family. Several reports about him, made during his life by specialists, were at our disposal. One of them states: "blood pressure 135/70"; another: "blood pressure 180/110 and very wide pupils" (!); a third says: ',pulsations of the heart so vehement that the table on which the patient lies, shakes synchronously".

III $M_{8\ ee}$, female, 50 years of age.

Extensively examined. No reasons for suspicion of phaeochromocytoma.

III M_9, male, deceased 1942, 33 years old.

Had no "trembles". Died under the diagnosis "carcinoma of the thyroid gland with skeletal metastases (X-ray) in right os ileum". Neither diagnostic excision nor obduction was done. No further data available.

III N_2, female, deceased 1928, 26 years old.

Her father, $II_{5\ et}$ (85 years) told us, that III N_2 had the same complaints as his first wife (II_5) and that this was usually called "the trembles". She, however, was said to have it in a mitigated form. A few hours after her first delivery she had a period of unconsciousness, after which an attack of convulsions occurred three times. Ten months later she died under the clinical picture of haemorrhagic diathesis. Anyway, it is remarkable that her husband III $N_{2\ et}$ told us that he had never noticed any symptom in his wife that could be connected with "the trembles". The information from her father and the occurrence of eclamptic-like symptoms in a woman of *this* family encourage us to say that phaeochromocytoma can still be considered as being likely.

IV P_3, male, 40 years old.

No complaints at all. Histamine test doubtful. The left kidney is situated lower than normal (intravenous pyelography). Catecholamines repeatedly normal. The investigations were not extended or intensified because we did not like to burden IV P_3, who feels quite well, with an idea of being ill.

IV R_1, female, deceased 1957, 30 years old.

Phaeochromocytoma most likely. Hetero-anamnesis: typical attacks that cannot be misunderstood. She died after caesarian section due to eclamptic convulsions, at the end of her first pregnancy (8 months), with the clinical picture of haemorrhagia cerebri. During pregnancy a saltless regimen had been prescribed to her. She had a small goitre.

IV R_2, female, 24 years old.

No complaints, no abnormal findings. One time the catecholamine excretion (per 24 hours) amounted to 225 μg; a second time to 60 μg per 24 hours.

IV S_1, male, 31 years old.

Bilateral phaeochromocytoma (see above: probandus).

IV S_2, male, 30 years old.

Typical history. Big tumour on the left adrenal was removed (Prof. Dr. *J.F. Nuboer*). Pathologic-anatomical examination (Prof. Dr. *A. de Minjer*): phaeochromocytoma. Still has vague symptoms now and then, the cause of which is not really clear. Remains under control.

IV T_1, female, 15 years old.

Slight debilitas mentis; speech defect. No complaints or symptoms of adrenal medullary hyperactivity. Examination: no abnormal findings. One time the amount of catecholamine excretion was 200 μg per 24 hours.

IV U_3, female, 15 years old.

Typical history of complaints. Tumour of hen-egg size was removed from the right adrenal (Prof. Dr. *J.F. Nuboer*). Pathologic-anatomical investigation (Prof. Dr. *A. de Minjer*): phaeochromocytoma.

In the remaining members of the family no deviations in the sense of eventual phaeochromocytoma could be detected. Signs of Recklinghausen's or Hippel-Lindau's disease were also absent in all the members of the family.

An examination of catecholamine excretion before and after administration of histamine, performed in 13 adults (non-patients) of the family, and in a control group of equal number (arbitrarily chosen people) did not result in any significant difference.

Discussion from a genetic point of view

Not much is known about the heredity and mode of inheritance of phaeochromocytoma. Neither in "Handbuch der Erbbiologie des Menschen" edited by *Günther Just* (1940), nor in "Human Genetics" by *Gates* (1948), nor in "Genetik des Menschen" by *von Verschuer* (1959) could we find any communication about the heredity of phaeochromocytoma.

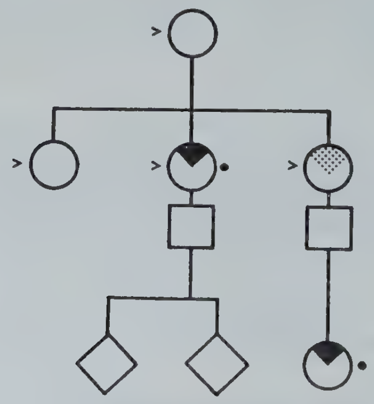


Fig. 2. *Calkins and Howard* (1947)

Prof. Dr. *Tage Kemp* (Copenhagen) wrote us that he himself had never seen a case of familial occurrence of phaeochromocytoma. *Graham* (10) found in a series of 207 cases familial occurrence in only one case. The first publication concerning the familial occurrence of phaeochromocytoma came (1947) from *Calkins and Howard* (1), who found two female patients in one family. The older one was an aunt of the younger one. The mother of the younger one raised in retrospect suspicion that she might have had the disease. Representation, see figure 2[1]).

Lohmann (2) in 1950 communicated the second case. Representation see figure 3.

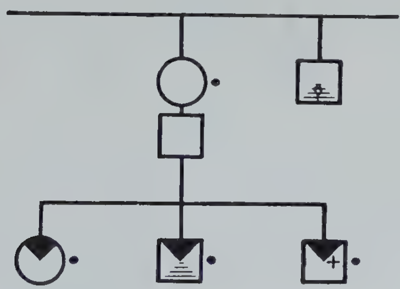


Fig. 3. *Lohmann* (1950)

In 1953 *Roth et al.* (3) published the 3rd case. Their findings are represented in figure 4.

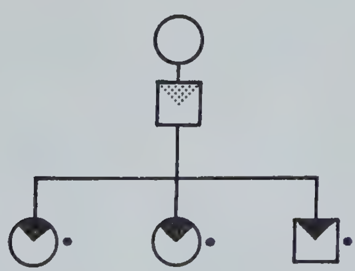


Fig. 4. *Roth, Hightower, Barker and Priestley* (1953)

Kelsall and Ross (4) in 1955 communicated the 4th case of familial occurrence. Representation, see figure 5.

1) We use the same signs as in the family tree (fig. 1). The sign > in fig. 2 means: thyreoidectomy.

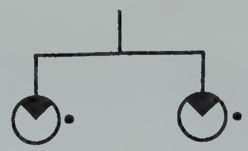


Fig. 5. *Kelsall and Ross* (1955)

Also in 1955 *Young and Murray* (5) published two cases in a family. See figure 6.

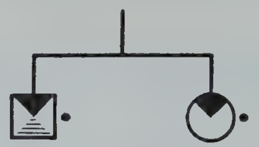


Fig. 6. *Young and Murray* (1955)

Cone et al. (6) published the 6th and 7th case in 1957. See figure 7 and 8.

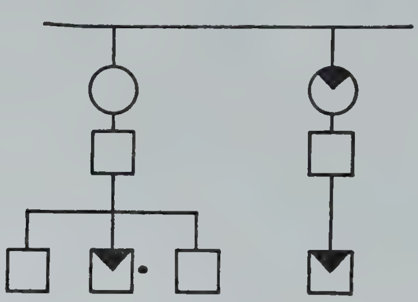


Fig. 7. *Cone, Allen and Pearson* (1957)

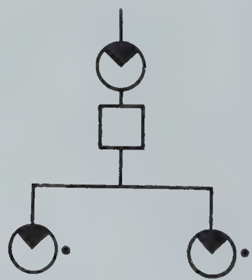


Fig. 8. *Cone, Allen and Pearson* (1957)

In 1959 *Greenberg and Gardner* (7) communicated the 8th case. Their extensive family tree is partially represented here (figure 9).

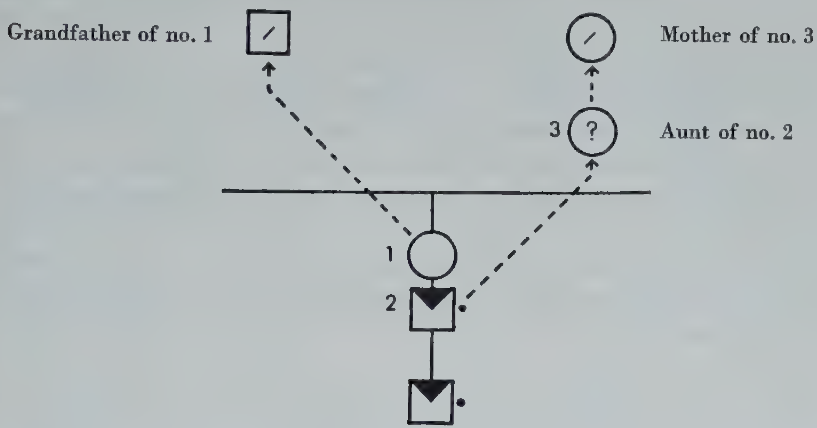


Fig. 9. *Greenberg and Gardner* (1959)

 and  are not-verified cases of hypertension. ? had verified hypertension, and the available data could be suspect for phaeochromocytoma, but are too scanty for representing this individual with a .

Cook et al. (8), reported phaeochromocytoma (malignant) occurring in a brother and sister in 1960. No further information about the family is given.

From the literature concerning the familial occurrence of phaeochromocytoma, which altogether comprises 24 definitely affected individuals, the following appears:

One of the parents of a phaeochromocytoma patient was affected with certainty in 4 cases; probably in 4 cases; only scanty data about the parents are available in 5 cases, and in 11 cases no data at all are at our disposal. No attention has been given to eventual consanguinity.

When reviewing the family we investigated, one can state:

a) The family tree concerns 87 persons: the „founder" of the family, I_1, 60 direct descendants and 26 allied by marriage, among whom was also the wife of I_1.

Of the 60 direct descendants, 20 were already deceased; of the remaining 40 persons, 39 were examined more or less extensively. One (IV P_1) could not be examined, due to his stay in the West Indies. Of the 26 allied by marriage, 4 were already deceased, 8 of them were examined. The 14 allied

by marriage of generation IV were not examined, as there was no stringent reason for it by now, for anamnestically there was not the slightest suspicion for the existence of phaeochromcytoma, nor was this the case in any of the individuals of generation V. About the 8 examined allied by marriage no important findings can be reported.

b) In total, 4 individuals had (verified) phaeochromocytoma: in 2 persons bilateral, and in 2 persons unilateral. In 10 persons, already deceased, the diagnosis phaeochromocytoma can be claimed as being likely.

c) One of the parents of all 4 verified cases has very likely suffered from the same disease.

d) Nine out of the 10 persons likely to have suffered from phaeochromocytoma, had one of their parents also probably affected. Of the parents of I_1 nothing is known.

Analysis of the pedigree and of the data derived from the literature

When we put together all certain and all probable cases of the family tree, the following table results:

Table 1

Patient × healthy individual	Number of children	Affected children	Healthy children	Children who died early	No data available
$I_1 \times I_1$ ee	8	2	–	6	–
$II_1 \times II_1$ee	9	6	3	–	–
$II_5 \times II_5$ et	3	1	1	1	–
III M_1 × III M_1 ee	3	–	3	–	–
III M_3 × III M_3 ee	2	1	1	–	–
III M_5 × III M_5 et	3	2	1	–	–
III M_7 × III M_7 et	2	–	2	–	–
III M_8 × III M_8 ee	4	1	2	1	–
III N_2 × III N_2 et	1	–	1	–	–
IV R_1 × IV R_1 et	1	–	1*	–	–
IV S_1 × IV S_1 ee	2	–	2*	–	–
IV S_2 × IV S_2 ee	1	–	1*	–	–
(Number of marriages) 12					
Total	39	13	18	8	–

Explanation: 1 miscarriage of about 2 months (mother III M_7) was not counted; 1 child, 8 months (of intra-uterinal life) old at the moment the mother (II_5) died, was counted among the early dead. The children marked with * are toddlers or babies.

When a table of cases mentioned in the literature (see above) is composed in the same way, the following list results:

Table 2

Patient × healthy individual	Number of children	Affected children	Healthy children	Children who died early	No data available
Calkins and Howard	2	–	–	–	2
Calkins and Howard	1	1	–	–	–
Roth et al.	3	3	–	–	–
Cone et al.	1	1	–	–	–
Cone et al.	2	2	–	–	–
Greenberg et al.	1	1	–	–	–
Total: 6	10	8	–	–	2

Concerning table 2 we must remark that the underlying material can be considered as being "selected" on the basis of the presence of the disease; this explains the high frequency of affected individuals in the descendants mentioned in this table. The difference with table 1 is that the latter, starting from a probandus, was obtained by investigating his whole family; table 2 was obtained by summarizing a number of families, each of which was published just because more than one case occurred in such a family. So, the results of both tables cannot be compared without considering this point.

When we put together the marriages of definitely affected individuals of our pedigree, we get the result as summarized in table 3.

Table 3

Patient × healthy individual	Number of children	Affected children	Healthy children	Children who died early	No data available
III M_1 × III M_1 ee	3	–	3	–	–
IV S_1 × IV S_1 ee	2	–	2*	–	–
IV S_2 × IV S_2 ee	1	–	1*	–	–
Total: 3	6	0	6	–	–

Children indicated with * are toddlers or babies.

Table 4 concerns the marriages of definitely affected persons mentioned in the literature.

Table 4

Patient × healthy individual	Number of children	Affected children	Healthy children	Children who died early	No data available
Calkins and Howard	2	–	–	–	2
Cone et al.	1	1	–	–	–
Cone et al.	2	2	–	–	–
Greenberg et al.	1	1	–	–	–
Total: 4	6	4	–	–	2

On the strength of the above information it may be hypothesized that phaeochromocytoma is a hereditary disease, whose mode of inheritance may be explained by considering the presence of one dominant gene as the aetiological factor. This hypothesis is based on the following considerations.

1. In "dominant hereditary diseases" a family tree shows more affected individuals than it does in recessive hereditary diseases, because only the homozygous recessive individuals are phenotypically ill. The fact that our pedigree shows a frequent occurrence of phaeochromocytoma in a family supports the opinion that one is dealing with a dominant factor.

2. In the case of a typically "dominant hereditary disease" one of the parents of the affected individual is always affected too. In the pedigree this situation most probably occurs in *all the cases.* In the literature reviewed 24 proven cases of phaeochromocytoma are mentioned. In 11 of these cases nothing is known about the parents. The remaining 13 patients can be divided as follows:

4 patients: one of the parents is affected (proven)
4 patients: one of the parents is probably affected
3 patients: "father suffered from 'sclerosis'" *(Lohmann)*
1 patient: parents "did not have hypertension" *(Cone et al.)*
1 patient: mother was thyreoidectomized *(Calkins and Howard)*

Thus, the scanty literary data do not present really sound arguments against the opinion that we are dealing here with dominancy.

3. On the basis of the hypothesis, healthy children of affected parents should have descendants who are also healthy in respect to the disease studied. In our pedigree this is the case (III M_2 und III N_1). The literature does not give the information necessary.

4. When a (complete) dominant abnormal gene is present in an individual (heterozygosity) and this person marries a healthy partner (a marriage with

a partner possessing the same dominant gene can be considered as a great exception), each of the immediate descendants has the chance 0.5 to be heterozygous for the locus concerned, i.e., to have the disease. Thus, it is most probable that among the descendants of such marriages 50% of the individuals are affected. In practice this figure will hardly ever be found exactly. If in our pedigree we add the proven cases and the cases that can be – in virtue of strong arguments – considered being probably affected, we find 13 out of 39 such descendants affected (table I) (33⅓%). Moreover, 8 of these 39 children died at early age, i.e., in general too young to develop the disease. Furthermore, it cannot be excluded that among the 18 remaining children, considered as being healthy at the moment of investigation, some future patients are hidden. The relative number of affected children found may be considered to be in accordance with the hypothesis of the presence of one dominant gene in cases of phaeochromocytoma.

In addition to arguments in favour of monomeric dominancy, arguments against recessivity as mode of inheritance in phaeochromocytoma are available:

1. If one recessive abnormal gene occurs (heterozygosity) in both parents, 0.25 of the children of these phenotypically normal parents have the chance to become ill. This does not occur in our pedigree. As far as the literature is concerned, the three patients of *Lohmann* had a healthy mother. About the father we only know that he died from "arteriosclerosis". Further data are not available. One of the two cases of *Cone* had parents "who did not have hypertension". This annotation is too poor to be of any value. In all the remaining cases, the patients had one of their parents either suspect of or suffering from (proven) phaeochromocytoma.

2. Phaeochromocytoma is a relatively rare disease. Even if one considers a recessive gene, it certainly will have a low frequency in a population. Only inbreeding would, eventually, lead to an increase of the incidence of phaeochromocytoma. In our pedigree consanguinity can certainly be excluded. The literature does not give any indication in this direction.

As phaeochromocytoma is known to occur in both sexes in the same frequency, *x*-chromosomal or *y*-chromosomal inheritance can be excluded.

It may be concluded that the observations available do not provide valid arguments against the view that phaeochromocytoma is a hereditary trait, based on the presence of a dominant autosomal gene.

The variability in the clinical picture (severe and alarming symptoms on one hand, but mitigated forms on the other hand) may be described as variable phenotypic expressions of the dominant gene involved. Up till now there is no reason to consider the penetrance as less than 100%, however.

Summary

On the basis of observations in a family comprising 4 histologically verified cases of phaeochromocytoma and 10 cases considered as having suffered most probably from the disease, it is hypothesized that phaeochromocytoma is a hereditary disease with a dominant autosomal mode of inheritance.

The literature concerning the familial occurrence of phaeochromocytoma is discussed.

Zusammenfassung

Auf Grund von Beobachtungen in einer Familie mit vier histologisch nachgewiesenen und zehn sehr wahrscheinlich aufgetretenen Fällen von Phäochromocytom ist anzunehmen, daß das Phäochromocytom eine erbliche Krankheit mit autosomal-dominantem Erbgang ist.

Die Literatur über familiäres Auftreten von Phäochromocytom wird diskutiert.

Résumé

Sur la base d'observations faites dans une famille comprenant 4 cas de phéochromocytome vérifiés histologiquement et 10 cas considérés comme ayant été très probablement atteints par l'affection, l'auteur émet l'hypothèse que le phéochromocytome est une affection héréditaire dotée d'un mode de transmission dominante autosomale.

Il passe également en revue la littérature concernant les atteintes familiales de l'affection.

REFERENCES

1. *Calkins, E. and Howard, J. E.:* Bilateral familial pheochromocytomata with paroxysmal hypertension: successful surgical removal of tumors in two cases, with discussion of certain diagnostic procedures and physiological considerations. J. clin. Endocrin. *7:* 475 (1947).
2. *Lohmann, V.:* Über Diabetes Mellitus bei Nebennierenmarktumoren. Dtsch. med. Wschr. *75:* 138 (1950).
3. *Roth, G. M.; Hightower, N. G.; Barker, N. W. and Priestley, J. T.:* Familial pheochromocytoma. Arch. Surg., Lond. *67:* 100 (1953).
4. *Kelsall, A. and Ross, E. J.:* Bilateral phaeochromocytoma in two sisters. Lancet *ii:* 273 (1955).

5. *Young, R.C. and Murray, W.A.:* Familial adrenal pheochromocytoma with sustained hypertension. Canad. med. Ass. J. *72:* 503 (1955).
6. *Cone, T.E.; Allen, M.S. and Pearson, H.A.:* Pheochromocytoma in children. Report of three familial cases in two unrelated families. Pediatrics *19:* 44 (1957).
7. *Greenberg, R.E. and Gardner, L.I.:* Pheochromocytoma in father and son: report of the eighth known affected kindred. J. clin. Endocrin. *19:* 351 (1959).
8. *Cook, J.E.; Urich, R.W.; Sample, H.G and Fawcett, N.W.:* Peculiar familial and malignant pheochromocytomas of the organs of Zuckerkandl. Ann. intern. Med. *52:* 126 (1960).
9. *Burn, G.P.:* Urinary excretion of the pressoramines in relation to phaeochromocytoma. Brit. med. J. *i:* 697 (1953).
10. *Graham, J.B.:* Pheochromocytoma and hypertension. An analysis of 207 cases. Collective review. Int. Abstr. Surg. *92:* 105 (1951).

Authors' addresses: Dr. M. Smits, Nicolaïlaan 19, *Bilthoven* (Netherland); Dr. J. Huizinga, Kromme Nieuwe Gracht 52A, *Utrecht* (Netherland)

Acta genet. *11:* 154–161 (1961)

From the Stomatological Department (Director: Prof. P. Adler, M.D.)
of the University Medical School, Debrecen, Hungary

CORRELATION BETWEEN THE DEVELOPMENT OF DIFFERENT TEETH

By L. NYUL and P. ADLER

In the development of single teeth several stages can easily be distinguished (as e. g., formation of the tooth bud, beginning calcification, finishing the crown formation, start of root growth, eruption, finishing root growth, etc.). Between the different tooth entities there are rather marked differences as to the age at which any defined phase of development occurs. In this way, the development of the total dentition may serve as a useful tool in assessing regularity of growth and development in youth, covering with the complete set of deciduous and permanent teeth a rather extended period in the individual's life. Certain stages of tooth development, as e. g. eruption, have often been studied; tooth eruption ages display a very marked variablility in the population.

Paying due attention to the two aforementioned items, as regards dental development one is wont to distinguish between, e.g. "early", (approximately) "average", and "late" eruptors. This concept was adopted by *Klein and Palmer* in demonstrating the dependence of caries prevalence figures on posteruptive tooth-age. For orthodontic purposes tables were constructed by one of the authors (A.), demonstrating typical tooth formulae with six months' age intervals of early, average, and late eruption in boys and girls. In these studies it was assumed on a logical basis that if a tooth erupts in an individual significantly earlier (or later) than at the average age, all other teeth are justifiably expected to behave in the same manner. According to this assumption, tooth eruption occurs – in spite of the marked standard deviations of the mean eruption ages –, in an "orderly manner". To the authors' knowledge this assumption has not been proven in a direct way formerly; an attempt was therefore made to check it. These studies are reported here.

Methods and material

There are two ways to solve our problem, viz.

(i) a longitudinal study, repeated examinations of the same children *at rather short intervals* through several years, in order to cover the eruption of different teeth; the intervals are necessarily in no instance longer than 3 months;

(ii) cross sectional study: assessment of the developmental stage of two or more teeth in the same child, at any (selected or non-selected) stage of dental eruption *in one instance*, with proper statistical treatment of the results.

With regard to difficulties encountered in longitudinal studies over several years, the second way was chosen.

A. In the first series intraoral dental roentgenograms were taken on usual size dental films in orthoradial projection from the (erupted) lower first permanent molar, and from the developing germs of the second molar and second premolar, in children of both sexes who had passed their 6^{th} but not their 7^{th} birthday. In Hungary primary school is entered by children who pass their 6^{th} birthday before September 1. School entrants were unselectedly X-rayed at their first visit in the School Dental Service of Debrecen, Hungary. Films were taken from approximately 470 children.

B. In the second series, approximately 130 children were x-rayed, the central beam being directed upon the region of the lower premolars (without regard to their being erupted or not), taking care that at least the mesial root of the erupted first permanent molar was visible on the film in its full length. In the sample the sexes are equally represented. The examinees were chosen from children who had passed their 9^{th} but not their 11^{th} birthday.

From these two series of roentgenograms, the suitable ones were selected for measurements. Measurements were carried out using a magnifying appliance (magnification approximately 1:2.2) and a vernier-scale. Those films were used only in which sharpness was sufficient at this magnification to permit measuring with 0.1 mm exactness. From the 470 films in the first series, only 96 were found eligible according to these rigid requirements. In the second series, exposures were continued of children visiting the school dental service until 100 suitable films were collected.

A. Measurements taken in the first series were:

(a) apical width of the first molar (M_1): distance between the dentinal walls at the apical end of the distal root;

(b) total length of M_1 from the occlusal surface to the apical end of distal root's dentinal wall;

(c) summarized length of the proximal enamel of M_1 – sum of the distance between mesial (distal) occlusal ridge and the cervical enamel border;

(d) the same summarized proximal enamel length of M_2 (second molar);

(e) and of P_2 (second premolar).

Measurements were grouped according to the apical width of M_1. It was expected that the total root length of M_1 might be inversely proportional to its apical width, while no connection was assumed between apical width and M_1 proximal enamel length since at the age of examinees crown formation of M_1 has been finished for some time. On the other hand, since crown development of M_2 and of P_2 is not yet finished, an inverse proportion was expected between the proximal enamel length of these teeth and the apical width of M_1.

B. Measurements taken in the second series are:

(f) total length of M_1, from the mesial occlusal ridge to the apical end of the mesial root's mesial dentinal wall;

(g) the maximum length of the second premolar form the occlusal surface to the most apical point of the root; and

(h) the maximum length of the first premolar (in the same manner).

Results of measurements were treated statistically. In series A means and standard errors were computed for the groups, formed arbitrarily in reliance upon the M_1 apical width, and differences of means were tested for statistical significance. In series B tables of correlation were set up, and coefficients of full (and of partial) correlation were computed.

Results. Means and standard errors of measurements b to e of *Series A*, in dependence on M_1 apical width shown in Table 1.

Table 1

Mean tooth length measurements in relation to the first molar's apical width

Apical width of the distal root of M_1	Number of x-rays	Distal root length of M_1	Mesial + distal enamel length of		
			M_1	P_2	M_2
1.0–1.5	20	14.55±0.74	10.78±0.62	9.43±0.56	10.79±0.63
1.5–2.0	37	13.45±0.46	10.80±0.37	9.51±0.32	10.66±0.38
>2.0	39	13.35±0.42	11.08±0.36	9.37±0.19	10.64±0.36

All measurements in mm.

Between the groups slight differences were found in the total length of M_1. Although shorter roots are associated with wider apical measurements, the differences are not statistically significant. As regards enamel length of M_1, means of group 1 and 2 agree well, but in group 3, unexpectedly, a higher mean value was obtained, the difference being statistically insignificant. In the second premolar's enamel length no regularity can be seen in our three groups, whereas in the second molar's enamel length a gradual decrease is obvious from group 1 to group 3, without statistical significance.

Since means of small biometrical series' are profoundly influenced by even one extraordinarily great or small measurement, examinees were classified within the aforementioned three groups (formed according to M_1 apical width) into two classes, according to whether the enamel length exceeded the arbitrary limit of 10 mm or not. Results summarized in Table 2 show a rather uniform distribution according to the enamel length of M_1 in the three groups. In the second premolar as well as in the second molar, however, frequency of examinees with enamel length over 10 mm decreases in the groups with greater M_1 apical widths. Without testing differences in the distributions statistically, the figures of Table 2 are indicative of the existence of a connection that was hitherto assumed for logical reasons.

Table 2

Distribution of examinees according to the sums of the mesial + distal enamel length

Tooth	Mesial + distal enamel length	Apical width of the M_1 distal root in mm		
		1.0–1.5	1.5–2.0	>2.0
M_1	Up to 10 mm	5 = 25%	9 = 24.3%	8 = 20.5%
	>10 mm	15 = 75%	28 = 75.7%	31 = 79.5%
P_2	Up to 10 mm	13 = 65%	25 = 67.6%	29 = 74.4%
	>10 mm	7 = 35%	12 = 32.4%	10 = 25.6%
M_2	Up to 10 mm	4 = 20%	9 = 24.3%	14 = 35.9%
	>10 mm	16 = 80%	28 = 75.7%	25 = 64.1%

The correlation table between the first and second premolar's length of *Series B* is shown in Table 3. A strong positive correlation was found between these variables ($r_{VY} = 0.868$).

Admitting the theoretical possibility that this strong positive correlation may be (at least partly) due to interindividual variations of tooth size, similar tables were constructed between the total length of M_1 (x), P_1 (y),

Table 3

Correlation between the first and second lower premolar's length

First premolar length in mm (y)	Second premolar length in mm (v)												
	3.1–4.0	4.1–5.0	5.1–6.0	6.1–7.0	7.1–8.0	8.1–9.0	9.1–10.0	10.1–11.0	11.1–12.0	12.1–13.0	13.1–14.0	14.1–15.0	15.1–16.0
5.1– 6.0	–	2	1	–	–	–	–	–	–	–	–	–	–
6.1– 7.0	1	–	–	3	–	–	–	–	–	–	–	–	–
7.1– 8.0	–	1	1	4	5	–	–	–	–	–	–	–	–
8.1– 9.0	–	3	3	1	5	2	–	–	–	–	–	–	–
9.1–10.0	–	–	1	5	3	3	4	3	–	–	–	–	–
10.1–11.0	–	–	–	–	6	2	8	2	3	–	–	–	–
11.1–12.0	–	–	–	–	1	1	4	1	1	1	–	–	–
12.1–13.0	–	–	–	–	–	–	–	1	3	–	–	–	1
13.1–14.0	–	–	–	–	–	–	–	2	–	2	–	–	–
14.1–15.0	–	–	–	–	–	–	–	–	1	1	2	2	–
15.1–16.0	–	–	–	–	–	–	–	–	–	–	–	1	1
16.1–17.0	–	–	–	–	–	–	–	–	–	–	1	–	1

$\bar{v} = 8.85$ mm $\sigma_v = 2.745$ mm

$\bar{y} = 10.16$ mm $\sigma_y = 2.417$ mm

$r_{vy} = 0.868$

and P_2 (v), respectively. The coefficients of correlation are $r_{xy} = 0.585$, and $r_{xv} = 0.552$. Being statistically significant, they are indicative of some mutual dependence that is not as strong as the correlation prevailing between the first and second premolar's length.

In order to assess the influence exerted by the third tooth on the interrelationship between the two others, with the three measurements of

Table 4

Coefficients of correlation, and of partial correlation between length of first molar (x), first premolar (y), and second premolar (v) in the lower jaw

Coefficient of correlation	r_{xy}	r_{xv}	r_{yv}
Numerical value	0.585	0.552	0.868
After *z* transformation	0.67	0.62	1.32
Standard error of *z*	0.101	0.101	0.101
Coefficient of partial correlation	$r_{xy.v}$	$r_{xv.y}$	$r_{yv.x}$
Numerical value	0.256	0.107	0.805
After *z* transformation	0.26	0.107	1.07
Standard error of *z*	0.102	0.102	0.102

Series B, partial correlation coefficients were computed also. Results are shown in Table 4. It is obvious that the correlative interdependence of P_1 and P_2 lenght is hardly influenced at all by the M_1 lenght. In contrast to this finding, the length of P_1 seems to exert a very profound influence on the correlation between M_1 and P_2 lenght. The partial correlation coefficient $r_{vx.y} = 0.107$ is not statistically significant although $r_{vx} = 0.552$ is statistically significant. Lenght of P_2 has a marked influence on the correlation between the length of M_1 and P_1: $r_{xy} = 0.585$, and $r_{xy.v} = 0.256$. Although this latter value is statistically significant (on the 5% level), it differs in a statistically significant way from the former coefficient.

Discussion

In Series A no conclusive evidence was obtained indicating that the development of the dentition follows a regular pattern. In Series B this seems cogently demonstrated.

First of all it seems necessary to analyse reasons for the "unsatisfactory" results in Series A. *A posteriori* it seems to us that the apical width of M_1 is perhaps not a reliable criterion for grouping as regards the developmental stage of this tooth. In children of 6 yrs 0 mo. to 6 yrs 11 mo. the first molar's development is well progressed, and in nearly all instances the apex was found to be just closed. A funnel-like apex (apical "foramen") was seen in a very few x-rays only. Variations of the M_1 apical width are, thus, rather limited. The apical width may be influenced by tooth-size also. Indicative of such an influence is our finding that greater M_1 enamel length was associated with larger M_1 apical width (Table 1). Furthermore, it seems questionable whether the proximal enamel length of tooth crowns being just formed is a measurement representing the developmental stage, inasmuch as in Table 1 the differences between the enamel lengths of M_1, M_2, and P_2 are rather small in all subgroups formed according to M_1 apical width. With regard to the results of Series B, we are prone to believe that measurements taken by us in Series A were not very suitable. One further item deserves attention. The time interval between the development of M_1 on the one hand, and of M_2 and P_2 on the other hand, is rather marked; it amounts to far more than four years as regards mean eruption ages.

With these considerations in mind, our Series B was started. Our prime purpose was the comparison of the first and second lower premolar's developmental stages. Between these two teeth, there is a much smaller interval in the mean eruption ages, amounting in boys to 0.73, in girls to 0.72 years (mean eruption ages are in boys 11.12 and 11.85, in girls 10.55

and 11.27 years, with standard deviations 1.31; 1.37; and 1.26; 1.39 years, as determined by *Adler* in a Hungarian provincial population characterized by low caries prevalence in the deciduous teeth), i.e., less than 9 months. Earlier eruption of P_1 was observed in this selected population (data for both sexes combined) in more than 80% of examinees, of P_2 in somewhat less than 10% (in the remaining 10% no decision could be made as to the eruption sequence of these teeth based on a single clinical examination). Summarizing, between the lower first and second permanent premolar there is some temporal difference in development.

In Series B, measurements of M_1 total length were taken also. In children who had passed their 9th birthday, we may justifiably expect that longitudinal root growth of M_1 is finished. Thus, M_1 length may represent tooth size attained after completed growth. It is interesting to see that size of M_1, as measured in the x-rays, displays a rather marked variability, and that it is statistically significantly correlated with the actual length of any premolar being in different stages of development. Coefficients of partial correlation disclosed that correlation between the first molar's length (a tooth with completed longitudinal growth) and the second premolar's length (this tooth is the most retarded in development in the three teeth examined) is reduced to a statistically insignificant value if the influence of P_1 length is excluded. P_2 exerts markedly less influence on the correlative interdependence between M_1 and P_1 lengths; it is to be noted that P_1 is 9 months in advance of P_2 in development, being thus at any stage nearer to its future complete length. These findings are in favour of the view that in the correlative interdependence of actual tooth size the developmental stage (expressed, e.g., in percentages of completed growth) may be the decisive factor.

Results of Series B indicate, as regards the correlation between P_1 and P_2 length, that what was assumed on logical grounds (i.e., the more advanced development of one tooth is associated with a more advanced developmental stage in other teeth in the individual) is really true. *Besides logical deductions, our findings are the first factual proof of this assumption.*

Judging from our results, it seems justifiable to classify a person by the developmental stage (e.g. eruption) of one single tooth as an "early", "average", or "late" toothdeveloper.

Summary

The developmental stages of two or more teeth were assessed on intraoral roentgenograms of the lower M_1, M_2, P_1, and P_2. A strong positive corre-

lation (r = 0.868) was found between the total length of the two premolars during development. By this strong correlation one can classify a person as early, average, or late in tooth development, using the developmental stage of one single tooth as a criterion.

Zusammenfassung

Es wurde der Entwicklungsstand von je zwei oder mehreren Zähnen an intraoralen Röntgenbildern der beiden untern bleibenden Molaren und Prämolaren verglichen. Eine stark positive Korrelation (r = 0,868) wurde zwischen der Länge der beiden Prämolaren während der Entwicklung nachgewiesen. Diese berechtigt, ein Kind auf Grund des Entwicklungsstandes eines einzigen Zahnes als «Früh-», «Durchschnitts-» oder «Spätzahner» in bezug auf das Gesamtgebiss zu klassifizieren.

Résumé

Comparaison de l'état de développement de deux ou plusieurs dents à l'aide de radiographies intra-orales des deux premières molaires et prémolaires. Les auteurs ont trouvé une corrélation positive très prononcée (r = 0,868) entre la longueur des deux prémolaires pendant le développement. Ceci permet de classer un enfant comme précoce, moyen ou tardif du développement dentaire, en se basant uniquement sur l'état de développement d'une seule dent comme critère.

REFERENCES

Adler, P.: Die Eignung der normalen Wahrscheinlichkeitskurve zur Darstellung der Elimination und Eruption der einzelnen Zähne während des Zahnwechsels. Öst. Z. Stomat. *54:* 449 (1957).

Klein, H. and Palmer, C.E.: Studies on dental caries. VI. Caries experience and variation in the time of eruption of the permanent teeth. Child Developm. *9:* 203 (1938).

Authors' address: Dr. L. Nyul and Prof. P. Adler, Stomatological Dept., University Medical School, *Debrecen* (Hungary).

Acta genet. *11:* 162–169 (1961)

Aus dem Seminar für Medizinische Statistik der Universität Marburg/Lahn
(Leiter: Prof. Dr. K. Solth)

INWIEWEIT STIMMEN DIE FINGERLEISTEN DER FAMILIENANGEHÖRIGEN ÜBEREIN?

Ein Beitrag zur genetischen Determination der Fingerleisten

Von K. SOLTH

Die verschiedenen Typen der Fingerleisten sind schon am Ende der foetalen Entwicklung vollständig ausgebildet. Um für die genetische Auswertung das Gesamtbild der Typen an den zehn Fingern erfassen zu können, wurde 1951 der «Individuelle Musterwert» von *Brodhage und Wendt* eingeführt. Die Berechnung dieses individuellen Musterwertes beruht auf einer Einteilung der Fingerleisten in 7 Typen. Diese Typen werden dann entsprechend dem Grade ihrer Komplexität mit laufenden Kennziffern versehen. Wird jedoch außer der Komplexität der Fingerleistentypen auch die Häufigkeit ihrer Vorkommen berücksichtigt, so ergeben sich andere Kennziffern *(Solth und Stecher)*. Durch diese letzteren Kennziffern ist es möglich, beide Eigenschaften, das heißt Komplexität und Häufigkeit der Fingerleisten, gleichzeitig auszudrücken.

		Rangordnung-Kennziffern nach	
		Komplexität	Komplexität und Häufigkeit
Bogen	B	1	3
Bogen-Schleifen	Bs	2	2
Schleifen-Bogen	Sb	3	6
Schleifen	S	4	28
Schleifen-Wirbel	Sw	5	20
Wirbel-Schleifen	Ws	6	30
Wirbel	W	7	42

Aus den für die 10 Finger einer Person ermittelten Kennziffern wird durch Addition der individuelle Musterwert gebildet. Bei dem individuellen Musterwert handelt es sich also um einen zwischen 10 und 70 (bei Bestimmung auf Grund der Komplexität allein) bzw. 20 und 420 (bei Berücksichtigung sowohl der Komplexität wie der Häufigkeit) liegenden

Zahlenwert, durch den eine Person oder eine Population hinsichtlich der Fingerleisten charakterisiert werden kann.

Obwohl die Fingerleisten an den zehn Fingern so individual spezifisch sind, daß das gleiche Gesamtmuster nie bei zwei Menschen vorkommt, zeigen erbbiologische Untersuchungen naturgemäß dennoch einen gewissen Grad von Übereinstimmung zwischen Eltern und Kindern. So konnte ein erheblicher Einfluß auf den individuellen Musterwert bei 348 Familien mit 991 Kindern von *Wendt* demonstriert werden. Irgendwelche begründeten Vorstellungen über den Erbgang wurden bisher nicht entwickelt, wie überhaupt das Problem vorläufig noch nicht völlig aufgeklärt ist.

Die vorliegende Arbeit hat zum Ziele, die bisherigen Untersuchungen am individuellen Musterwert durch Berechnung der Korrelationen zwischen Eltern und Kindern zu erweitern. Durch den Korrelationskoeffizienten soll eine eventuelle Übereinstimmung zwischen Eltern und Kindern hinsichtlich der Fingerleisten ermittelt werden.

Unseren Untersuchungen liegen Familien mit jeweils mindestens zwei Kindern zu Grunde. Es handelt sich um 246 Elternpaare mit 628 Kindern (davon 314 Söhne und 314 Töchter). Das Material, welches uns Herr Prof. *Wendt* (Dozentur für Anthropologie am Anatomischen Institut) zur Verfügung gestellt hat, wurde für Erblichkeitsuntersuchungen an Fingerleisten unter dem Gesichtspunkt größtmöglicher Sicherheit gesammelt; es stammt nicht aus erbbiologischen Begutachtungen.

Bei der Ermittlung der verschiedenen Eltern-Kind-Korrelationen haben wir die Wechselbeziehung sowohl für den auf Grund der Komplexitäts-Kennziffern zusammengestellten individuellen Musterwert wie für den auf Grund der Komplexitäts und Häufigkeits-Kennziffern zustandegekommenen individuellen Musterwert berechnet. Da die Komplexitäts- und Häufigkeitskennziffern für jede Person zwei Eigenschaften repräsentieren und zufolge des heterogeneren Merkmals eine größere Variation der Untersuchten darstellen, werden die Korrelationen jener Musterwerte, die mit Hilfe der Komplexität und Häufigkeit der Fingerleisten errechnet worden sind, selbstverständlich kleiner sein als die Korrelationen, welche die Wechselbeziehung hinsichtlich nur eines einzigen Merkmals, das heißt der Komplexität ausdrücken. Wenn die ersteren Korrelationen dennoch statistisch gesichert werden können, ist dies ein Existenzbeweis a fortiori.

Um herauszufinden, ob die elterlichen und kindlichen Fingerleisten überhaupt und inwieweit übereinstimmen, haben wir zunächst die Korrelation zwischen den Durchschnitten der elterlichen und kindlichen Musterwerte und erst später die entsprechenden Korrelationen zwischen den Musterwerten jedes Elternpaares und jedes Kindes bestimmt. Bei dieser zwei-

fachen Bestimmung sind wir von der Annahme ausgegangen, daß die «Gesamterbanlage» aller Kinder der der Eltern mehr ähneln dürfte als die stärker variierende Erbanlage der einzelnen Kinder.

Außer an den Korrelationsgrößen zwischen den Musterwerten waren wir auch an den entsprechenden Regressionslinien interessiert. Eine geradlinige Regression bedeutet nämlich nach *Penrose* das Vorhandensein von additiven Genen und das Fehlen von Dominanz –, dagegen läßt die Abweichung von der Geradlinigkeit entsprechend der Richtung der Divergenz das Vorhandensein von Dominanz oder rezessiven Eigenschaften vermuten. Um daher das Vorhandensein von additiven Genen bzw. von dominanten oder rezessiven Eigenschaften feststellen zu können, haben wir die betreffenden sinnvollen Regressionen – das heißt jene von Eltern zu Kindern – auf ihre Geradlinigkeit bzw. auf ihre Abweichung von der Geradlinigkeit durch das Verhältnis $r/\eta_x = r_{x.k}$ *(Solth)* geprüft.

Da bei einer linearen Regression $r = \eta_x$ ist, darf der Korrelationskoeffizient der Klassendurchschnittswerte $r_{x.k}$ – wenn auch nicht im strengen Sinne – als Richtmaß für die Geradlinigkeit der untersuchten Wechselbeziehung gelten. Bei vollkommener Linearität der Regressionslinien ist also $r_{x.k} = 1{,}0$. Je mehr die Regressionslinien von einer Geraden abweichen, desto mehr unter 1,0 liegt der Wert $r_{x.k}$ – wobei jedoch über die Art der Abweichung eine Aussage nur auf Grund der Inspektion des Regressionsdiagramms möglich ist.

Zuerst haben wir untersucht, ob nicht zwischen Vätern und Müttern hinsichtlich des individuellen Musterwertes ein Zusammenhang besteht – was vom sachlichen her zwar nicht begründbar, aber nichtsdestoweniger möglich erscheint. Die betreffenden Korrelationskoeffizienten waren bei den 246 Vätern und Müttern die folgenden:

für Komplexität allein $r = -0{,}0516 \pm 0{,}0636$
für Komplexität und Häufigkeit $r = -0{,}0886 \pm 0{,}0633$

Entsprechend der Erwartung konnten wir also zwischen Vätern und Müttern keinerlei signifikante Korrelation hinsichtlich des individuellen Musterwertes feststellen. Auch *Holt* gab bei 149 Familien eine Interparental-Korrelation von $0{,}05 \pm 0{,}08$ an.

Dagegen fanden wir, daß die Durchschnitte der individuellen Musterwerte der 246 Eltern und ihrer Kinder eine große Übereinstimmung aufweisen:

für Komplexität allein $r = +0{,}7318 \pm 0{,}0296$, mit $r_{x.k} = 0{,}9788$, wodurch eine lineare Regression rechtens angenommen werden kann.

für Komplexität und Häufigkeit $r = +0{,}6049 \pm 0{,}0404$, mit $r_{x.k} = 0{,}8208$.

Die Eltern-Kinder-Korrelation beträgt bei den Untersuchungen von *Holt* $0{,}69 \pm 0{,}03$. Die Fingerleistentypen, dargestellt durch den individuellen

Musterwert, sind also geerbt, und in der Erbanlage der Kinder wirken additive Gene wahrscheinlich mit.

Es lag auf der Hand, nach der Korrelation zwischen Vätern und Müttern sowie zwischen Eltern und Kindern auch zu fragen, inwieweit sich die Geschwister selbst hinsichtlich des individuellen Musterwertes zueinander ähneln. Zur Beantwortung haben wir den Zusammenhang zwischen den Musterwerten von Söhnen und Töchtern untersucht. 152 Familien hatten sowohl Söhne wie Töchter; die Korrelationskoeffizienten beziehen sich also auf 152 Angabenpaare, wobei im Falle 2 oder mehrerer Söhne oder Töchter in einer Familie der Durchschnitt der Musterwerte genommen wurde. Die erhaltenen Korrelationskoeffizienten:

für Komplexität allein $r = +\,0{,}4389 \pm 0{,}0654$
für Komplexität und Häufigkeit $r = +\,0{,}3753 \pm 0{,}0696$

befinden sich erheblich unter den Korrelationsgrößen zwischen Eltern und Kindern, das heißt, daß Vorkommen von gleichen Musterwerten bei den Geschwistern bedeutend seltener ist als zwischen Eltern und Kindern. Dieser Unterschied ist statistisch gesichert.

Wegen dieser ausgeprägten Differenzen zwischen den drei obigen Familienangehörigen-Gruppen ergab sich die Frage, ob die Übereinstimmung hinsichtlich des individuellen Musterwertes zwischen jeweils einem Elter und den Söhnen bzw. zwischen jeweils einem Elter und den Töchtern immer dieselbe oder eine unterschiedliche ist. Um diese Frage beantworten zu können, haben wir die Korrelation zwischen Vätern und Söhnen bzw. Töchtern, und die Korrelation zwischen Müttern und Söhnen bzw. Töchtern bestimmt. Diese Korrelation haben wir wegen der sehr variierenden Musterwerte der Kinder nicht nur in bezug auf alle Söhne bzw. Töchter einer Familie (das heißt für Durchschnitte der kindlichen Musterwerte), sondern auch in bezug auf jedes einzelne Kind (das heißt für alle einzelnen Musterwerte der Söhne und Töchter) errechnet.

Betrachten wir zuerst die Übereinstimmung zwischen Vätern bzw. Müttern und allen Söhnen einer Familie (das heißt bei einem Musterwert-Durchschnitt für alle Söhne einer Familie), dann ergeben sich für die 202 Familien mit Söhnen die folgenden Korrelationskoeffizienten:

1. Zwischen Vätern und allen Söhnen einer Familie

für Komplexität allein $r = +\,0{,}4858 \pm 0{,}0537$, mit $r_{x.k} = 0{,}9283$;
für Komplexität und Häufigkeit $r = +\,0{,}4281 \pm 0{,}0575$, mit $r_{x.k} = 0{,}8346$.

2. Zwischen Müttern und allen Söhnen einer Familie

für Komplexität allein $r = +\,0{,}4186 \pm 0{,}0580$, mit $r_{x.k} = 0{,}8615$;
für Komplexität und Häufigkeit $r = +\,0{,}3193 \pm 0{,}0632$, mit $r_{x.k} = 0{,}8595$.

Wenn wir die individuellen Musterwerte von jedem einzelnen der 314 Söhne mit den Musterwerten der Väter bzw. Mütter in Beziehung bringen, dann verändern sich die Korrelationskoeffizienten nur geringfügig:

1. Zwischen Vätern und den einzelnen Söhnen:
für Komplexität allein $r = +0{,}4427 \pm 0{,}0450$, mit $r_{x.k} = 0{,}8971$;
für Komplexität und Häufigkeit $r = +0{,}3813 \pm 0{,}0482$, mit $r_{x.k} = 0{,}7694$.

2. Zwischen Müttern und den einzelnen Söhnen:
für Komplexität allein $r = +0{,}4073 \pm 0{,}0470$, mit $r_{x.k} = 0{,}8115$;
für Komplexität und Häufigkeit $r = +0{,}3286 \pm 0{,}0503$, mit $r_{x.k} = 0{,}8692$.

Nach den erhaltenen Korrelationskoeffizienten, das heißt nach den erwiesenen Maßen des Grades der Gleichheit oder Ungleichheit zwischen den beobachteten Paaren ist das Ergebnis der Untersuchung dahin zu interpretieren, daß die Ähnlichkeit hinsichtlich der individuellen Musterwerte zwischen Vätern und Söhnen größer ist als zwischen Müttern und Söhnen. Ganz abgesehen davon, ob wir den individuellen Musterwert von allen Söhnen einer Familie im Durchschnitt oder von jedem Sohn im einzelnen dem individuellen Musterwert der Väter bzw. Mütter gegenüberstellen, kommt bei den ermittelten Korrelationen etwa der gleiche Unterschied zum Vorschein. Allerdings sind die Unterschiede in keinem der vier Vergleichspaare statistisch gesichert (t-Werte zwischen 0,54 und 1,27).

Wenn wir dieselbe Gegenüberstellung zwischen Töchtern und Vätern bzw. Müttern vornehmen – von den 246 Familien waren Töchter in 195 –, gestalten sich die Korrelationskoeffizienten folgendermaßen:

1. Zwischen Vätern und allen Töchtern einer Familie:
für Komplexität allein $r = +0{,}4724 \pm 0{,}0556$, mit $r_{x.k} = 0{,}9198$;
für Komplexität und Häufigkeit $r = +0{,}3942 \pm 0{,}0605$, mit $r_{x.k} = 0{,}9131$.

2. Zwischen Müttern und allen Töchtern einer Familie:
für Komplexität allein $r = +0{,}3583 \pm 0{,}0624$, mit $r_{x.k} = 0{,}9016$;
für Komplexität und Häufigkeit $r = +0{,}2612 \pm 0{,}0667$, mit $r_{x.k} = 0{,}7256$.

Gleichfalls haben wir den Zusammenhang zwischen den Musterwerten der Väter bzw. Mütter und denen der einzelnen 314 Töchter bestimmt, um den Effekt der sehr streuenden individuellen Musterwerte der Kinder auf die untersuchte Übereinstimmung berücksichtigen zu können.

1. Zwischen Vätern und den einzelnen Töchtern:
für Komplexität allein $r = +0{,}4383 \pm 0{,}0456$, mit $r_{x.k} = 0{,}9004$;
für Komplexität und Häufigkeit $r = +0{,}3786 \pm 0{,}0483$, mit $r_{x.k} = 0{,}7942$.

2. Zwischen Müttern und den einzelnen Töchtern:
für Komplexität allein $r = +0{,}3773 \pm 0{,}0480$, mit $r_{x.k} = 0{,}8932$;
für Komplexität und Häufigkeit $r = +0{,}3133 \pm 0{,}0509$, mit $r_{x.k} = 0{,}7994$.

Wiederum scheint in bezug auf die Fingerleistenstruktur eine größere Ähnlichkeit zwischen Vätern und Töchtern vorhanden zu sein, als zwischen Müttern und Töchtern. Leider sind auch diesmal die Korrelationen der Väter von denen der Mütter statistisch nicht genügend (t-Werte zwischen 0,92 und 1,47) unterschiedlich.

Diese Feststellungen, die nochmals mit den Befunden von *Holt* übereinstimmen, weisen nicht auf einen extra mütterlichen (das heißt uterinalen) Effekt bei der Entwicklung der Fingerleisten hin.

Obwohl der Korrelationskoeffizient bloß eine mathematische Interpretation der Wechselbeziehung zwischen zwei Variablen ist – ohne jegliche Andeutung einer möglichen Ursache –, kann der Vergleich einer Reihe von Korrelationskoeffizienten doch gewisse Informationen geben, besonders dann, wenn diese Zusammenhangbestimmungen aus einem Material stammen, in dem erbliche Abhängigkeit variiert.

Eine Erläuterung unserer Ergebnisse ermöglichen uns die von *R.A. Fisher und Penrose* errechneten theoretischen Korrelationsgrößen. Nach den Erwägungen dieser Autoren sollte die Korrelation zwischen Eltern und Kindern theoretisch 0,5 sein, wenn additive Gene in der Erbanlage mitwirken. Die Korrelationen zwischen den Eltern- und Kinder-Durchschnittswerten sollten dagegen theoretisch eine Größe von $1/\sqrt{2} = 0{,}71$ sein.

Betrachten wir im Falle der Komplexitätsmusterwerte den Zusammenhang zwischen den Durchschnittswerten beider Elternpartner und den Durchschnittswerten aller Kinder, so finden wir, daß diese Korrelationsgröße ($r = 0{,}7318$) dem theoretischen Wert von 0,71 ziemlich gut entspricht. Auch die Regressionslinie von Eltern zu Kindern ist in diesem Falle annehmbar geradlinig ($r_{x.k} = 0{,}9788$). Von hier aus angesehen spricht also nichts dagegen, daß die Vererbung der Fingerleistenstruktur über das Zusammenwirken von additiven Genen erfolgt.

Bei der Gegenüberstellung der einzelnen Elternpartner und der einzelnen Kinder liegen dagegen die Korrelationswerte unter dem theoretischen Korrelationswert von 0,5 (nämlich zwischen 0,26 und 0,48). Auch die betreffenden Regressionen von Eltern zu Kindern sind in keinem Fall mit Sicherheit geradlinig ($r_{x.k}$-Werte zwischen 0,7256 und 0,9283). Nach diesem Befund hin sollte also angenommen werden können, daß bei der Vererbung der Fingerleistenstrukturen auch dominierende bzw. rezessive, das heißt nicht ausschließlich additive Gene mitwirken.

Die ähnlichen Unterschiede zwischen den Korrelationen, die auf Grund der Komplexitäts- und Häufigkeitsmusterwerte berechnet wurden, erhärten noch mehr diese Schlußfolgerungen.

Der Erbgang der Fingerleisten ist also polyfaktoriell und recht kompliziert.

Zusammenfassung

Durch Bestimmung der Korrelationen zwischen den individuellen Musterwerten der Fingerleisten bei Familienangehörigen war es möglich, über den Erbgang dieser anatomischen Struktur annähernde Auskünfte zu erhalten. Während zwischen Vätern und Müttern erwartungsgemäß keine Korrelation bestand, ergab sich zwischen dem Durchschnittsmusterwert der beiden Eltern und dem aller Kinder eine Ähnlichkeitskorrelation von 0,7318, die dem theoretischen Wert von 0,71 voll entspricht. Dagegen lagen die Korrelationen bei den alternativen Gegenüberstellungen von Vätern bzw. Müttern mit Söhnen bzw. Töchtern im Bereich von 0,26–0,48 zum Teil erheblich unterhalb der theoretischen Erwartung von 0,50. Das Ergebnis der Untersuchung wurde dahin interpretiert, daß neben additiven Genen auch dominierende bzw. rezessive Gene bei Vererbung der Fingerleisten von Bedeutung sind.

Summary

By determination of the correlations between the individual pattern-values of the finger-ridges among the members of a family it was possible to obtain approximate informations about the way of inheritance of these anatomical structures. Whereas according to expectation no correlation existed between fathers and mothers, a likeness-correlation of 0,7318 resulted from the comparison of the pattern-averages of both parents and those of all children. This correlation corresponds completely to the theoretical value of 0,71. On the other hand the correlations of the alternate confrontations of fathers resp. mothers with sons resp. daughters ranged from 0,26 to 0,48, thus partly considerable under the theoretical expectation of 0,50. The result of the investigation can be interpreted in that way that beside additive genes also dominant resp. recessive genes have an important part in the inheritance of the finger-ridges.

Résumé

En déterminant les corrélations des valeurs types individuelles de la structure des empreintes digitales chez les membres d'une famille, on parvient à en tirer des renseignements approximatifs sur la transmission héréditaire de cette structure anatomique. Tandis que naturellement on ne trouve pas une corrélation entre la structure des empreintes digitales chez

les pères et les mères, le résultat entre la valeur type moyenne des deux parents et celle de tous leurs enfants est une corrélation d'analogie de 0,7318, qui correspond entièrement à la valeur théorique de 0,71. Par contre les corrélations se trouvaient en partie considérablement au-dessous de la valeur de 0,50 qu'on attendait théoriquement, lorsqu'on comparait alternativement les pères respectivement les mères, les fils respectivement les filles dans le champ de 0,26–0,48. Le résultat de cette recherche s'explique ainsi: à côté des gênes additifs, les gênes dominants respectivement récessifs ont une influence sur la transmission héréditaire de la structure des empreintes digitales.

LITERATUR

Brodhage, G. und Wendt, G.G.: Verwendung qualitativer Fingerleistensmerkmale in Vaterschaftsgutachten. Z. menschl. Vererb. KonstitLehre *30:* 221–241 (1951).

Fisher, R.A.: The correlation between relatives on the supposition of Mendelian inheritance. Trans. Roy. Soc. Edinb. *52:* 399–433 (1918).

Holt, Sarah B.: Genetics of dermal ridges: Parent-child correlations for total finger ridge-count. Ann. hum. Genet. *20:* 270–281 (1956).

Holt, Sarah B.: Quantitative genetics of dermal ridge-patterns on fingers. Acta genet. *6:* 473–476 (1956/57).

Penrose, L.S.: The biology of mental defect. (Sidgwick and Jackson, London 1949).

Solth, K.: Der Korrelationskoeffizient der Klassendurchschnittswerte als deskriptives Maß für Abschätzung der Linearität einer Regression. Ärztl. Forsch. *14:* I/290–I/292 (1960).

Solth, K. und Stecher, R.: Eine kombinierte Kennziffer für den «Individuellen Musterwert» der Fingerleisten. Z. Morph. Anthrop. (im Druck).

Wendt, G.G.: Der individuelle Musterwert der Fingerleisten und seine Vererbung. Acta genet. gemellolog. *4:* 330–337 (1955).

Adresse des Autors: Prof. Dr. K. Solth, Robert-Koch-Strasse 8a, *Marburg*/Lahn (Deutschland)

Acta genet. *11:* 170–177 (1961)

From the Institute of Human Genetics, University of Oslo, Norway, and the Department of Medicine, University of California School of Medicine, San Francisco, California

THE Gm(r) SERUM GROUP

By BRITA BRANDTZÆG, HUGH FUDENBERG and JAN MOHR

Introduction

At least four Gm-factors have previously been recognized, namely Gm(a), Gm(b), Gm(x) and Gm-like. The first three have now been studied in a considerable number of individuals and in families, with respect to the individual factors, and partly also with respect to their interrelations (*Brandtzaeg, B. and Mohr, J.*, 1961; *Grubb, R. and Laurell, A.B.*, 1956; *Harboe, M.*, 1959; *Harboe, M. and Lundevall, J.*, 1959; *Linnet-Jepsen, P.*; *Galatius-Jensen, F. and Hauge, M.*, 1958; *Moullec, J.; Kherumian, R.; Sutton, E. et Espagnon, P.*, 1956; *Mäkelä, O. and Tiilikainen, A.*, 1959). Concerning the Gm-like factor, however, observations are still not extensive (*Steinberg, A.C.; Giles, B.D. and Stauffer, R.*, 1960), and its relation, if any, to the other Gm-factors is not yet clear. The same applies to the recently discovered socalled In V factor (*Ropartz, Lenoir, Rivat*, 1961).

This paper concerns an additional component of the Gm-system, discovered by one of us (H.F.), and tentatively termed Gm(r).

The purpose of the present study is to evaluate the distribution of Gm(r) in unrelated and related individuals, and its biochemical basis, particularly whether Gm(r):

1. shows monomeric, penetrant inheritance, like the other Gm-factors;
2. shows any relation to the other Gm-factors, and if so, what kind of relationship;
3. concerns the same small molecular component of the gamma globulin as do Gm(a), Gm(b) and Gm(x), and if the level of gamma globulin differs with Gm-types.

Material

The material comprises 323 unrelated individuals and 95 complete families with 348 children; 223 are Norwegians, whereof 200 are parents

from the family material, while the remaining 100 are Americans. The families were selected on the basis of having at least two children.

Methods

The technique used is nearly the same as the one previously described (*Brandtzaeg, B. and Mohr, J.*, 1961). The red cells were coated with incomplete anti-D Ham., kindly supplied by Dr. *A.G. Steinberg*, Western Reserve University, Cleveland, Ohio. One volume of packed red cells was added to one volume of anti-D serum and four volumes of saline. The mixture was incubated at 37°C for about one and a half hours. The anti-Gm(r) serum used for all the typings was Cal. The titer of this serum against coated red cells was 1:256. Positive and negative controls, as well as saline controls, were used for all the sera tested.

For the individuals typed by *Fudenberg*, the technique used was only slightly different.

Results

1. *Unrelated individuals.* Of the 323 unrelated individuals tested, 193 were Gm(a). Among the Gm(a) individuals, 173, or 89.6%, were Gm(r). All Gm($\overline{a}$) individuals were Gm($\overline{r}$). The results are given in table 1.

Table 1

Distribution of Gm(r) in 323 unrelated individuals

Gm(a)		Gm($\overline{a}$)		
Gm(r)	Gm($\overline{r}$)	Gm(r)	Gm($\overline{r}$)	Total
173	20	0	130	323

2. *Family material.* The distribution of Gm(r) was studied in 95 Norwegian families with a total of 348 children. In 15 of these families with a total of 62 children, both parents and all children were Gm($\overline{r}$); the distribution in the remaining families is shown in tables 2 and 3.

3. *Gamma Globulin isolation and quantitation.* It appears that the Gm(r) property is confined to the 7S portion of the gamma globulin; this was demonstrated by titration of fractions obtained from starch block electro-

Table 2

Distribution of Gm(r) in 52 families of mating type Gm(r) × Gm($\overline{\text{r}}$)

r = number of children of recessive type Gm ($\overline{\text{r}}$)	c = number of children in family tested for Gm(r) 1	2	3	4	5	6	7	8	9	10	11	Total
0	–	1	11	2	–	–	–	–	–	–	–	14
1	–	2	9	1	–	–	–	–	–	–	–	12
2	–	–	8	5	1	1	–	–	–	–	1	16
3	–	–	4	2	1	–	–	–	–	–	–	7
4	–	–	–	2	1	–	–	–	–	–	–	3
Total	–	3	32	12	3	1	–	–	–	–	1	52

Table 3

Distribution of Gm(r) in 28 families of mating type Gm(r) × Gm(r)

r = number of children of recessive type Gm($\overline{\text{r}}$)	c = number of children in family tested for Gm(r) 1	2	3	4	5	Total
0	–	–	7	4	2	13
1	–	1	3	5	3	12
2	–	–	1	2	–	3
Total	–	1	11	11	5	28

phoresis and density gradient ultracentrifugation; Gm(a), Gm(b) and Gm(x) are also confined to the 7S gamma globulin (*Fudenberg, H.*, 1961).

Gamma globulin levels were measured in 100 random sera by a modified zinc turbidity reaction (*Fudenberg, H., German, J.L. and Kunkel, H.G.*, 1961). No significant differences were observed in Gm(ar), Gm(a$\overline{\text{r}}$) and Gm($\overline{\text{ar}}$) sera; the mean levels were 42.1, 43.4 and 42.3 turbidity units, respectively (normal: 36 to 49 units).

Discussion

1. *Reliability of the tests.* In about one-tenth of the sera tested, the reaction was not satisfactory the first time, although by repeated testing sufficiently good reactions were achieved to permit classification as positive

or negative. With the sera available, the Gm(r) testing was thus not so straightforward as in general for the Gm(a) typing.

2. *Frequency among unrelated individuals.* Of 323 unrelated individuals 173 were found to be Gm(r). The gene frequency is thus:

$$f(Gm^{r}) = 1 - f(Gm^{\bar{r}}) = 1 - 0.6814 = 0.3186.$$

3. *Mode of inheritance of the Gm(r) factor.* The hypothesis of "dominant single factor inheritance of the Gm(r) factor was tested according to the method described by *C. A. B. Smith.* The observed numbers are recorded in table 2 for families of mating type Gm(r) $\times$ Gm($\bar{r}$), and in table 3 for matings of the Gm(r) $\times$ Gm(r) type. The figures in column r and row c represent the numbers of families observed to have c children tested for Gm(r), r of them being recessives. The observed and expected number of recessives are shown in tables 4 and 5. From table 4 it appears that the agreement between the observed and expected number of children within each category is close ($\chi^2 = 0.019$ with 1 d. f., $P = 0.89$). In the case of the Gm(r) $\times$ Gm(r) families, the agreement is fair ($\chi^2 = 2.067$ with 1 d. f. $P = 0.16$. The observed number of families with at least one recessive child is also compared with the expected number of such families as calculated from the total number of families in the sample. The estimate of the gene frequency

Table 4

Families of mating type Gm(r) $\times$ Gm($\bar{r}$)

Number of children in family (c)	Number of families m_c	Observed number of recessives	Expected number of recessives $m_c a_c$	Variance $m_c b_c$
2	2	2	2.666	0.444
3	21	37	36.000	10.286
4	10	25	21.333	7.820
5	3	9	7.743	3.246
6	1	2	3.048	1.379
11	1	2	5.503	2.737
Total	38	77	76.293	25.912

$\chi^2 = 0.019$ with 1 d.f. $\quad P = 0.89$

Table 5

Families of mating type Gm(r) × Gm(r)

Number of children in family (c)	Number of families M_c	Observed number of recessives	Expected number of recessives M_cA_c	Variance M_cB_c
2	1	1	1.143	0.122
3	4	5	5.188	1.052
4	7	9	10.241	2.940
5	3	3	4.917	1.776
Total	15	18	21.489	5.890

$\chi^2 = 2.067$ with 1 d.f. P = 0.16

Table 6

Families of mating type Gm(r) × Gm($\overline{r}$)

Number of children in family (c)	Total number of families n_c	Number of families with at least one recessive child Observed m_c	Expected n_cud_c	Variance $n_cud_c\ (1-ud_c)$
2	3	2	1.821	0.716
3	32	21	22.666	6.612
4	12	10	9.112	2.193
5	3	3	2.353	0.507
6	1	1	0.797	0.162
11	1	1	0.810	0.154
Total	52	$\sum m_c = 38$	37.559	10.344

$\chi^2 = 0.019$ with 1 d.f. P = 0.89

$Gm^r = 0.32$ has been used for the calculations presented in tables 6 and 7. Also, in the case of this comparison, the agreement is good. For the Gm(r) × Gm($\overline{r}$) families, $\chi^2 = 0.019$ with 1 d. f., P = 0.89 and for the Gm(r) × Gm(r) families, $\chi^2 = 1.44$ with 1 d. f., P = 0.23. In table 8, all the χ^2 for the different comparisons and the different mating types are added together ($\chi^2 = 3.55$ with 4 d. f., P = 0.47).

Table 7

Families of mating type Gm(r) × Gm(r)

Number of children in family (c)	Total number of families N_c	Number of families with at least one recessive child		
		Observed M_c	Expected $N_c u^2 D_c$	Variance $N_c u^2 D_c (1-u^2 D_c)$
2	1	1	0.287	0.205
3	11	4	4.167	2.589
4	11	7	4.930	2.720
5	5	3	2.500	1.250
Total	28	$\sum M_c = 15$	11.884	6.764

$\chi^2 = 1.44$ with 1 d.f. $\quad$ P = 0.23

Table 8

Combined χ^2 for the comparisons in tables 4, 5, 6 and 7

Test	Mating	χ^2	D.F.
Number of recessive children given m_c	Gm(r) × Gm($\bar{r}$)	0.02	1
Number of recessive children given M_c	Gm(r) × Gm(r)	2.07	1
m_c given n_c	Gm(r) × Gm($\bar{r}$)	0.02	1
M_c given N_c	Gm(r) × Gm(r)	1.44	1
Total		3.55	4

$\chi^2 = 3.55$ with 4 d.f. $\quad$ P = 0.47

Information obtained on six additional families by one of us (H.F.) is also compatible with the hypothesis that the Gm(r) factor is determined by a "dominant" allele at the Gm locus.

4. *Relation to Gm(a).* Among 690 tested individuals (including the family material) 375 were Gm(ar), 38 Gm(a$\bar{r}$), 277 Gm($\overline{ar}$); in other words, not a single Gm($\bar{a}$r) was found. From this it may be calculated, with 95% confidence, that the true frequency of Gm($\bar{a}$r) individuals, if this type occurs at all, does not exceed 0.43%.

Summary

A new human hereditary gamma globulin group (Gm group), tentatively designated Gm(r) is described. The Gm(r) factor was studied in a total of 690 individuals, including 95 families with 348 children. The distribution was found to be compatible with monomeric penetrant inheritance of the

Gm(r) factor. The gene frequency was estimated to be 0.3186. Gm(r) was observed in 90% of 413 Gm(a) individuals, and in none of the Gm($\bar{a}$) individuals.

The Gm(r) property was demonstrated to be confined to the 7S portion of the gamma globulin, like Gm(a), Gm(b) and Gm(x). No significant differences were observed between gamma globulin levels of Gm(ar), Gm(a$\bar{r}$) and Gm($\overline{ar}$) sera.

Zusammenfassung

Es wurde eine neue erbliche Gamma-Globulin-Gruppe (Gm-Gruppe) beim Menschen beschrieben und vorläufig Gm(r) genannt. Der Gm(r)-Faktor wurde bei 690 Personen untersucht, darunter 95 Familien mit 348 Kindern. Die Verteilung erwies sich als verträglich mit dem monomeren Erbgang des Gm-Faktors. Die Genhäufigkeit wurde mit 0,3186 angegeben. Gm(r) wurde bei 90% von 413 Gm(a)-Personen, jedoch bei keiner Gm($\bar{a}$)-Person beobachtet. Man zeigte, daß die Gm(r)-Eigenschaft auf den 7S-Anteil des Gamma-Globulins beschränkt ist, wie Gamma(a), Gamma(b) und Gamma(x). Signifikante Unterschiede zwischen den Gammaglobulinspiegeln von Gm(a$\bar{r}$), Gm($\overline{ar}$) und Gm(ar)-Seren wurden nicht beobachtet.

Résumé

Un nouveau groupe de gamma-globuline héréditaire chez l'homme (groupe Gm) appelé provisoirement Gm(r) est décrit. Ce facteur est étudié chez 690 individus comprenant 95 familles de 348 enfants. La distribution correspond à un unique gène pénétrant du facteur Gm(r). La fréquence du gène est évalué à 0,3186.

Le Gm(r) a été observé chez 90% de 413 Gm(a) individuels et jamais dans ceux du type Gm($\bar{a}$). Le caractère Gm(r) est inhérent à la portion 7S de la gamma-globuline, en analogie avec Gm(a), Gm(b) et Gm(x). On n'a pas constaté de différences significatives entre le taux de gamma-globuline des Gm($\overline{ar}$), Gm(ar) et Gm($\overline{ar}$).

ACKNOWLEDGEMENTS

Thanks are due to Dr. *A. G. Steinberg* for generous gifts of anti-D Ham.

REFERENCES

Brandtzaeg, B. and Mohr, J.: On the genetics of the Gm serum system. Acta genet. *11:* 111–125 (1961).

Fudenberg, H.: (in preparation, 1961).

Fudenberg, H.; German, J.L. and Kunkel, H.G.: Arth. Rheumat. (in press)

Grubb, R. and Laurell, A.B.: Hereditary serological human serum groups. Acta path. microbiol. scand. *39:* 390–398 (1956).

Harboe, M.: A new haemagglutinating substance in the Gm-system, anti-Gm^b. Acta path. microbiol. scand. *47:* 191–198 (1959).

Harboe, M. and Lundevall, J.: A new type in the Gm-system. Acta path. microbiol. scand. *45:* 357–370 (1959).

Linnet-Jepsen, P.; Galatius-Jensen, F. and Hauge, M.: On the inheritance of the Gm serum group. Acta genet. *8:* 164–196 (1958).

Moullec, J.; Kherumian, R.; Sutton, E. et Espagnon, P.: Contribution à l'étude du facteur de groupe Gm^a du plasma humain. Rev. Hémat. *11:* 512–517 (1956).

Mäkelä, O. and Tiilikainen, A.: Inheritance of the Gm serum group. Ann. Med. exp. Fenn. *37:* 180 (1959).

Ropartz, C.; Lenoir, J. and Rivat, L.: A new inheritable property of human sera: The In V factor. Nature *189:* 586 (1961).

Smith, C.A.B.: A test for segregation ratios in family data. Ann. Eugen., Lond. *20:* 257–265 (1956).

Steinberg, A.C.; Giles, B.D. and Stauffer, R.: A Gm-like factor present in Negroes and rare or absent in Whites. Its relation to Gm^a and Gm^x. Amer. J. hum. Genet. *12:* 44–51 (1960).

Authors' addresses: Dr. B. Brandtzaeg and Dr. J. Mohr, Institute of Human Genetics, University, *Oslo* (Norway); Dr. H. Fudenberg, Department of Medicine, University of California School of Medicine, *San Francisco*, Calif. (USA)

LETTER TO THE EDITOR

In the paper by *F. Vogel* „Eine Tafel für den Vergleich zweier Häufigkeitsziffern bei seltenen Ergebnissen" (Acta genet. *9:* 314–319 [1959], a method has been outlined and a table given which is well suited for this purpose. I would just like to draw attention to a table for the same purpose, published previously by *Hald* (1952). The two parts of this table give the 2.5% and the 0.5% one-sided limits. In the notation of *Vogel* n_1 und n_2 are the sizes of the two samples, and i_1 und i_2 are the number of cases found in the two samples.

When the lower limit is wanted the notation of *Hald* is as follows:

$$\vartheta = \frac{n_1}{n_1 + n_2} \qquad n\text{–}x = i_1 \qquad x = i_2$$

In the column n–x it is then noted where the greater number of the pair shifts from a value lower to a value greater than ϑ. The corresponding value of x is then the lower limit of i_2.

When the upper limit is sought the notation of *Hald* is

$$\vartheta = \frac{n_1}{n_1 + n_2} \qquad x = i_1 \qquad n\text{–}x = i_2$$

In the row, x, it is noted where the greater number of the pair shifts from a value greater to a value lower than ϑ. The corresponding value of n–x is then the greater limit of i_2.

Another table which may be used for the same purpose is no. $VIII_1$ in *Fisher and Yates* (1957). This table is, however, more complicated to use than the tables of *Vogel and Hald.*

References:

Fisher, R.A. and Yates, F.: Statistical tables for biological, agricultural and medical research (Oliver and Boyd, Edinburgh 1957).

Hald, A.: Statistical tables and formulas (Wiley, New York 1952).

Arne Nielsen, Copenhagen

LIBRI

Sonderausschuss Radioaktivität Bundesrepublik Deutschland. Zweiter Bericht (März 1959). Georg Thieme Verlag, Stuttgart 1959. 117 p., kartoniert DM 12.60.

Measurements of radioactivity in air, rainfall, water and foodstuffs for the period November 1957–October 1958 from a series of German institutions are recorded. Since the issue of the first report in January 1958, the stations for the measurement of radioactivity in Germany have been substantially expanded and the measurements systematized which was not the case in the first period of measurement, October 1956–October 1957. In the new report, the material in the tables has been increased by 300 per cent, the number of pages by 70 per cent and the price by 120 per cent.

The average radioactivity in the air has apparently remained unchanged since the first report while the radioactivity in rainfall and dust and also water has decreased slightly but, on the other hand, a slight increase in the ^{90} Sr content of milk is recorded. These results were compared with results from other countries, in particular the United Kingdom, USA and USSR and the figures appear to be of similar magnitude.

In addition, a series of measurements on imported foodstuffs are reported and it was demonstrated that the ^{90} Sr content of cheese from Scandinavia is considerably higher than in cheese from a series of mediterranean countries and from East Africa. Further, a particularly high ^{90} Sr content in vegetable products from East Asia was demonstrated. It is concluded that the immediate danger from the ^{90} Sr content is slight but even if atomic bomb experiments cease at once, the strontium content of the earth will, nevertheless, increase to thrice its present value in the course of 10–15 years and will thereafter decrease. If experiments with nuclear weapons continue unchanged, the ^{90} Sr content of the earth will increase in the course of 150 years about 50 times to approximately 350 mc/km^2 and thereafter probably attain a value of equilibrium.

The new report is not only as the first merely mentioning the problem of contamination but it also gives the results of measurements concerning individuals exposed to occupational radiation. Individuals working with radioactive substances appear to be exposed to a dosage twice as great as that to which individuals working with X-ray radiation are exposed and ten per cent receive more than the permitted maximal dosage. The authors of the present report promise that subsequent reports will deal with sources of radiation not produced by contamination and, in particular, investigations concerning medically induced radiation dangers have been instituted. *B. Zachau-Christiansen*, Copenhagen

H. P. G. Seckel: **Bird Headed Dwarfs.** Studies in Developmental Anthropology, Including Human Proportions. S. Karger, Basel/New York 1960. VIII + 241 p., 64 fig., S.Fr. 54.–.

The author of the present monograph, who is professor of pediatrics at the University of Chicago, has longitudinally observed 2 dwarfs and described them in detail. Furthermore he records 24 cases from the literature.

On the basis of these studies, he presents a special dwarf-type which is characterized by extreme statural shortness, dwarfish size of head and brain, special "bird-headed" facial characteristics, and mental retardation. Neither the clinical, nor the pathological-anatomical examination showed any endocrine disturbances, whereas the disease seems to have

familial occurrence. Section of the brains showed nothing structurally abnormal. The patients matured sexually, but in no cases did they reproduce. These patients are born dwarfish at full term; the smallest weighed 500 g at birth and measured 18 cm.

The author has undertaken detailed anthropological measurements and has found that these dwarfs' overall proportions were those of a "miniature human being", i.e. they had the same proportions as normals at the same age. The disease is often combined with congenital malformations of different types, reminiscent of syndromes like Franceschetti's syndrome, mongolism, amniotic amputations, pancytopenia of the Fanconi-type etc. An excellent differential diagnostic survey is given. The author thinks that the disease is a recessively hereditary one.

An enormous work has been undertaken in going through the literature, and in the anthropological investigations. The book will be of great value to everyone who is occupied with dwarfism. The studies were concluded before the later chromosomal investigations turned out to be of current interest; this ought, of course, to be included in future investigations in this field. *Jakob Øster*, Randers (Denmark)

H. Harris: **Human Biochemical Genetics.** Cambridge University Press, London 1959. 310 pages. 37 sh. 6d.

The study of the inborn enzyme defects and their clinical, genetic and biochemical picture now plays a central role in human genetics. The chromosomal DNA substance is thought to be the template for the formation of the protein molecules and perhaps primarily of different enzymes, and the study of the gene – enzyme relationship must at present be considered as fundamental in genetics. Dr. Harris in his book gives a well balanced, up to date survey of the research in this intriguing field with an exhaustive and critical review of the literature. The book is extremely well written and the style so fascinating, that the reader is imperceptively introduced into the most complicated biochemical relations. Most exciting are the chapters dealing with Ingram's clarification of the structural differences between haemoglobin A, S and C, and Morgan's & Watkin's studies of the biochemical base of the A, B, H and Le^a blood group characters. These investigations have brought genetic research to a level very near to those macromolecular structures which classical genetics named genes.

The book is objective and inspiring at the same time and it will certainly prove indispensable as a text book for all students of human genetics. Besides it will find a natural place in the hospital library as a remedy for the clinician in his orientation in the jungle of inborn errors of metabolism. *B. Harvald*, Copenhagen

Stanley M. Garn: **Readings on Race.** C. C. Thomas, Springfield, III. 1960. 281 p. $ 6.75.

The book consists of selected articles on different aspects of race and race formation in man. The intention is to give an idea of the recent advances in the study of man. *Garn* describes his work as "a casebook rather than a text-book".

The articles deal with definition of race, sizes of human populations, climate and race, evolutionary factors as selection, genetic drift and migration and finally experimental studies of physiological differences between races.

Some of the articles are important theoretical contributions fairly well-known to anthropologists and human geneticists and it may be useful to have them collected in one book. *L. Beckman*, Uppsala

J.A.Fraser Roberts: **An Introduction to Medical Genetic .** 2nd Edition. Oxford University Press, London/New York/Toronto 1959. VIII + 263 p. 35s.

A textbook of high quality, addressing senior students and postgraduates. The study of the difficult theory of genetics is facilitated by the author's extraordinary pedagogic power. Obviously it has been the aim besides the theoretical principles to give guidance in the application of genetic theory to the practical eugenic problems, and the importance of different topics is evaluated from this point of view. The technique and psychology of eugenic advising has been condidered in a clever and wellbalanced way. The book is terminated by a reference to literature for further study. Without any doubt, however, the majority of students will not reach further in their study of genetics and for the sake of these readers a systematic revue of the mode of inheritance of different monomeric syndromes should perhaps have been included, besides a survey of the empirical chances in different clinical entities of probably multifactorial inheritance *B. Harvald*, Copenhagen

Laurence Picken: **The Organization of Cells and Other Organisms.** Clarendon Press, Oxford University Press, Oxford 1960. Pp. xxxvii + 629. 84 sh.

In this volume Professor *Picken* has tried to make a whole out of the innumerable observations within the fields of fundamental biological research. The author has indeed succeeded in his task. He has collected a vast number of facts from almost every branch of science concerned with biological problems: biochemistry, physical chemistry, genetics, electronmicroscopy, X-ray diffraction examination and light-microscopy in its most modern forms.

The book is very systematically built up. From a section on old and modern cell concepts it proceeds via a description of virus to the cell structure, devoting one or more chapters to each detail such as mitochondria, chloroplaste, pyrenoids, the Golgi region etc.

It is worth mentioning that the book particularly applies to the reader interested in general biology, it is not a medical textbook. But the geneticist who – inspired by the recent advances in cytogenetics – wants information on basic cellular phenomena will in this book have a most valuable volume of reference. The bibliography contains some 1600 numbers. The illustrations, 34 plates and 133 text-figures, are eminent. The book will find a place in many scientific libraries. *Anders Frøland*, Copenhagen

Curt Stern: **Principles of Human Genetics.** 2nd Edition. Freeman & Co., San Francisco 1960. X + 753 p., 265 ill., 125 tables. $9.50.

The scope of human genetics is growing broader, touching so different subjects as embryology, serology, forensic medicine, anthropology, medicine, biochemistry, sociology and even history. The wide-screen picture of this heterogenous landscape given by Professor *Stern* in his second edition of "Principles of Human Genetics" is highly successful, combining the expert's mastery of the detail with the master's breadth of outlook. The book is fascinating in several ways: first, by its highly didactic form it leaves the reader with the impression of having comprehended the most intricate genetic ideas (at the same time as the "problems" following each chapter will lead him back to a more realistic apprehension of his own situation!); secondly, the sober scientific way in which all topics are treated does away with the impression of a mere textbook and inspires to further research.

Obviously it is the aim of the author only to outline the general laws and principles of human genetics, referring to the specific problems concerning different hereditary traits

and diseases only as examples. A comprehensive subject index will, however, to some extent meet this need.

The book is too extensive for use in undergraduate medical teaching, and, furthermore, it needs a systematic part. On the other hand, it is the ideal textbook for the postgraduate student who wants to do some research work which brings him in contact with genetic problems. The good lists of references will conveniently lead the student to the central points in the current literature of human genetics. *Bent Harvald*, Copenhagen

D. P. Murphy and H. Abbey: **Cancer in Families.** A Study of the Relatives of 200 Breast Cancer Probands. Harvard University Press, Cambridge, Mass. 1959. Pp. X+76. 48 tables. $2.50.

The present study has derived an advantage from the previous similar investigations of the occurrence of cancer among the relatives of cancer patients by taking the criticism of these into account. The data were brought together during two periods. In the first of these, from 1949–1952, data on female relatives were collected, and in the second, from 1953–1955, data on male relatives as well as some new information about the females were obtained. The cancer probands were 200 white women aged 40–65 years, who had been treated for breast cancer in 28 hospitals of Philadelphia, whereas the 200 white female control probands were patients of the same age groups, seen in a dental clinic. No further matching was planned. The information about the family was obtained by personal interviews with the proband and one or more of her relatives, and the data were later checked by means of the files of hospitals, private practitioners, bureaus of vital statistics, undertakers and cemetery officials. The relatives investigated were the parents, the sibs of the parents as well as the spouses and the children of these relatives.

The analysis of the material may be divided into two parts. First, it is intended to show that the cancer groups and the control groups probably do not deviate from each other with regard to the characteristics which influence the frequency of cancer. Secondly, the frequencies of cancer and especially of breast cancer in the two groups are compared. It is concluded that if a familial tendency to develop cancer did exist, it was not large enough to be detected in a study of the present size. A comparison between the frequency of cancer in the relatives and that in the general population was not carried out.

Arne Nielsen, Copenhagen

D. S. Falconer: **Introduction to Quantitative Genetics.** Oliver & Boyd, Edinburgh 1960. 365 p., 61 fig., 37 tables. 35 sh.

The subject of the present volume is quantitative genetics which as stated in the introduction is dealing with "the inheritance of those differences between individuals that are of degree rather than of kind". But as quantitative differences usually depend on gene differences at many loci, the methods of Mendelian analysis are inappropriate, and the study must be extended to larger groups of individuals comprising many progenies; the subject may, therefore, equally well be described as what is called population genetics. This means that the immediate value of the volume may seem limited to human geneticists at the present stage of development, also because a number of chapters are devoted entirely to the most appropriate methods of selection, inbreeding and crossbreeding in experiments.

The title indicates that the present volume is an introduction. Therefore, the central problems are treated very broadly which gives the reader time to become familiar with

the thoughts and ideas. As an example of this may be mentioned the explanation of the important idea "the dispersive process". First, this is regarded as a sampling process and described in terms of sampling variance; secondly, it is regarded as an inbreeding process and described in terms of the genotypic changes resulting from matings between related individuals. In this way the reader gets a good general view in a short time, which is usually only achieved by means of much more time-consuming studies. As a rule, only the most important results are given, and the reader is referred to the relevant literature for the details, which are just briefly mentioned. It is impossible to read the book without some elementary knowledge of Mendelian genetics, statistics and especially the calculus of probability. The results are given as mathematical expressions, which is unavoidable when the subject is quantitative genetics. More complicated formulae occur only rarely, and the reasoning behind can be followed by anyone who can read a formula. A useful glossary of symbols is included.

The book is highly recommended as a very valuable help to the human geneticist who wants to study the principles and problems of quantitative and population genetics.

Arne Nielsen, Copenhagen

A Symposium on Cytology and Cell Culture Genetics of Man has recently been published with the aid of funds from the National Institutes of Health, Public Health Service, U.S. Departement of Health, Education and Welfare. Copies of this report may be obtained (free of charge) upon request from Dr. *Gordon Allen*, Building10 Room 2N208, National Institutes of Health, Bethesda 14, Maryland. The symposium is 42 pages in length and contains papers by *E.H.Y.Chu*, *C.E.Ford*, *M.L.Barr*, *L.Sachs and M.Krim* and by *M.Fraccaro.*

W. Lenz: **Medizinische Genetik.** Georg Thieme Verlag 1961. VIII+197 Seiten. 66 Abbildungen. DM 23.–

This is an introduction to medical genetics which is primarily written for medical students. It gives a full account of the elementary principles, based on the latest developments and with special emphasis on the biochemical background of human heredity. The author has been able to condense the material considerably without being in any way superficial, and the extensive use of examples taken from medicine brings the account into very close contact with the range of ideas of the medical profession. It has not been attempted to give a complete survey of the hereditary diseases, but a number of pathological conditions are touched on and a chapter has been included which deals with a few of the more common, genetically influenced diseases in greater detail. It should be mentioned that the methodological problems are also treated briefly, and the author has thus succeeded in producing a book which gives all people in the medical profession a short, but good introduction to medical genetics, and the bibliographies following each chapter make it easier to find the more complete accounts of the various subjects.

Mogens Hauge, Copenhagen

P.B.Medawar: **The Future of Man.** Methuen and Co. Ltd. London 1959. Pp. 128. 10s. 6d.

The six Reith Lectures given by Professor Medawar in the BBC during the winter of 1959 have been published, supplemented by a great number of notes, addressed to a professional audience. The lectures expound the reasoning underlying the predictions

about man's future, whereas no prophetic statements are attempted. After having come to the conclusion that man is still potentially capable of further evolution Professor Medawar discusses the forces which are changing the genetic make-up of human populations, and the kind of knowledge and understanding we must acquire about mankind, if we are to identify and predict the changes. Two systems of heredity are defined and extensively dealt with by the author: the endosomatic, genetical heredity which we have in common with other animals, and the exosomatic inheritance or non-genetic heredity, that is peculiarly our own and which is mediated through the transfer of information through non-genetic channels from one generation to the next. Professor *Medawar* specifically draws attention to the differences between these two systems, which have often been overlooked, and emphazises that „our policies and intentions are not to be based upon the supposition that nature knows best; that we are at the mercy of natural laws, and flout them at our peril". The possibilities of our improving nature depend upon "our continuing to explore into nature and to enlarge our knowledge and understanding of what is going on."
Mogens Hauge, Copenhagen

Bentley Glass: **Science and Liberal Education.** Louisiana State University Press, Baton Rouge 1959. Pp. X + 115. $3.00.

Professor *Glass* is in the three essays of this book preoccupied with much the same problems as outlined above. His main theme is the role and importance of science in human society. Examples taken from genetics are used to illustrate the immense power being given to man through the development of science, the great benefits which may result from the use of this power as well as the risks and quandaries implied. It is stressed that all the foresight and intelligence will have to be exercised to channel our newfound power into wise uses. To that end our „exosomatic inheritance" has to be increased and extended very considerably. Professor *Glass* points out that science must permeate all kinds of study and teaching to ensure a more widerspread understanding of the possibilities and problems of the present and the future. The deeply interesting relation between science, evolution and human values is discussed in the final part of the book.

Mogens Hauge, Copenhagen

G.E.W. Wolstenholme and C.M.O'Connor (ed.): **Biochemistry of Human Genetics.** J. & A. Churchill Ltd., London 1959. Pp. XII + 347. 50s.

A brillant account of some of the most fascinating parts of modern human genetics is given in this report of a Ciba Foundation Symposium. The subjects surveyed and discussed by experts include the hereditary enzyme deficiencies, the haemoglobins, myoglobin and plasma protein variants, the immunochemistry of the products of the blood group genes and the biosynthesis of blood group substances, and the application of tissue culture methods to this field of human genetics. A perfect index of subjects makes the book very useful and easy to consult. No genetic laboratory can do without this book.

M. Hauge, Copenhagen

PRIMATOLOGIA

HANDBUCH DER PRIMATENKUNDE
HANDBOOK OF PRIMATOLOGY
MANUEL DE PRIMATOLOGIE

HERAUSGEGEBEN VON EDITED BY RÉDIGÉ PAR

H. HOFER GIESSEN **A.H. SCHULTZ** ZÜRICH **D. STARCK** FRANKFURT

VOL. IV
LIEFERUNG 5: Vertebral Column and Thorax

By A. H. Schultz, Zürich
66 p., 28 fig., 17 tab., 1961. sFr. 20.—

Contents: Introduction – Vertebral column: Numbers of vertebrae – Relative lengths of spinal regions – Relative size of vertebrae – Some special features of: Cervical vertebrae, Sacral vertebrae, Caudal vertebrae – Curvature of vertebral column – Position of vertebral column in relation to thorax and to pelvis. Thorax: Shape of entire thorax and of ribs – Number of sternal ribs – Sternum – Literature.

VOL. II/1
LIEFERUNG 3: Volarhaut der Hände und Füße

Von J. Biegert, Zürich
VI+326 p., 101 fig., 58 tab. 1961. sFr. 75.—

Inhaltsverzeichnis: Allgemeiner Teil. – Historisches. Material. Einführung – Definition der Volarhaut - Volarballen: Phylogenetisches, Ballengrundplan von Hand und Fuß – Beugefurchen – Leistenhaut: Phylogenetisches, Histologie – Embryonale Beziehungen zwischen Ballen und Hautleistenanordnung – Klassifizierung der Hautleistenmuster – Musterintensität (P.I.). Verlauf der Leistenströme –Wertungsschlüssel.

Systematischer Teil. – I. Prosimiae: Tupaiiformes – Lemuriformes – Lorisiformes – Tarsiiformes. – II. Simiae: Platyrrhina (Cebidae, Callithricidae) – Catarrhina (Cercopithecoidea, Hominoidea). – Literaturverzeichnis.

BASEL (Schweiz) S. KARGER NEW YORK

L 49